COMPARATIVE STUDY ON EFFICACY, SAFETY AND TOLERABILITY OF ORAL METHOTREXATEAND ORAL AZATHIOPRINE IN CHRONIC PLAQUE PSORIASIS

This dissertation is submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

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M.D BRANCH XX

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DECLARATION

I solemnly declare that the dissertation titled "**COMPARATIVE STUDY ON EFFICACY, SAFETY AND TOLERABILITY OF ORAL METHOTREXATE AND ORAL AZATHIOPRINE IN CHRONIC PLAQUE PSORIASIS"** was done by me at **Stanley Medical College during 2012- 2015** under the guidance and supervision of my chief **Dr.V.Anandan, M.D (Derm).,**

The dissertation is submitted to **The Tamilnadu Dr.M.G.R. Medical University** towards the partial fulfilment of requirement for the award of **M.D. Degree – Branch XX in DERMATOLOGY, VENEREOLOGY AND LEPROSY.**

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CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled "**COMPARATIVE STUDY ON EFFICACY, SAFETY AND TOLERABILITY OF ORAL METHOTREXATE AND ORAL AZATHIOPRINE IN CHRONIC PLAQUE PSORIASIS** is a bonafide research work done by **Dr.V.SRIDHAR** under my guidance in partial fulfilment of the requirement of the award for the degree of **M.D Dermatology, Venereology & Leprosy** .

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This is to certify that the dissertation titled "**COMPARATIVE STUDY ON EFFICACY, SAFETY AND TOLERABILITY OF ORAL METHOTREXATE AND ORAL AZATHIOPRINE IN CHRONIC PLAQUE PSORIASIS"** is submitted by **Dr.V.SRIDHAR** to **The Tamilnadu Dr.M.G.R Medical University, Chennai** in partial fulfilment of the requirement of the award for the degree of **M.D BRANCH XX (DERMATOLOGY,VENEREOLOGY AND LEPROSY)** and is a bonafide work done by him.

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CONTENTS

ABSTRACT

OBJECTIVES: To assess the efficacy, safety and tolerability of T. methotrexate 15mg/wk and T.azathioprine 50mg/day in chronic plaque psoriasis.

INTRODUCTION:
Psoriasis is a common, chronic, and recurrent inflammatory disease of the skin. It has a tendency to wax and wane with flares related to systemic or environmental factors including life stress events and infection. Psoriasis is characterised by the infiltration of skin by activated T cells and an abnormal proliferation of keratinocytes. A classic lesion of psoriasis is characterised by well demarcated, raised, red plaques of varying sizes with a white scaly surface. Psoriasis also shows its impact on quality of life and potentially long term survival.

Methotrexate: Methotrexate has a greater affinity for dihydrofolic acid reductase than has folic acid. The synthesis of DNA is blocked when dihydrofolic acid reductase is bound and thereby cell division is reduced. Methotrexate may also affect the inflammatory element of psoriasis.

Azathioprine: Azathioprine is an immunosuppressive drug which is converted non-enzymatically in the body to 6-mercaptopurine (6-MP), then by hypoxanthine guanine phosphoribosyl transferase (HGPRT) to 6-thioguanine nucleotides. Their immunosuppressive activity results from disruption of normal DNA and RNA synthesis. Additionally, an imidazole metabolite appears to have powerful anti-inflammatory properties.

METHODS AND MATEIALS:

PLACE OF STUDY : Govt. Stanley medical college ,Chennai.
TYPE OF STUDY : RANDOMISED, PROSPECTIVE, OPEN LABEL, PARALLEL GROUP STUDY.
TIME DURATION : One year.(June 2013 to May 2014)
SAMPLE SIZE : 2 groups , each containing 20 patients.
STUDY PROCEDURE:
A brief and relevant medical history with physical examination will be taken at screening visit to ensure all the relevant eligibility criteria are met. After successful screening, patient would be randomised to one of the two treatment groups as follows,
GROUP A: Patients who fulfil inclusion criteria and willing to take part in trial and sign consent letter would be included in the study. They would be administered T.METHOTREXATE 15mg/week for 12 weeks. Efficacy will be

assessed by monitoring PASI score every week. Safety and tolerability monitored by complete hemogram weekly and liver function test biweekly. GROUP B: Patients who fulfil inclusion criteria and willing to take part in trial and sign consent letter would be included in the study. They would be administered T.AZATHIOPRINE 50mg/day for 12 weeks. Efficacy will be assessed by monitoring PASI score every week. Safety and tolerability monitored by complete hemogram weekly and liver function test biweekly.

CONCLUSION: Methrotrexate was found to be more efficacious than azathioprine in achieving PASI 75 at week 12. Both the drugs were safer and tolerable while remission period in the Methotrexate group was longer than Azathioprine group.

KEY WORDS: Psoriasis, Methotrexate, Azathioprine

INTRODUCTION

Psoriasis is a genetically determined, chronic inflammatory and proliferative, intractable skin disorder in which both environmental and genetic factors play vital role. It can cause severe discomfort, disfigurement and psychological distress to the affected.

Various treatment modalities for Psoriasis are available in this modern era. Treatment options usually based on the severity of disease, associated co-morbidities, efficacy and also patient preference. Severity of disease is clinically graded as mild to moderate, or moderate to severe. Patients with mild to moderate disease can be managed by topical therapy, while more severe disease requires systemic therapy.

Psoriasis is a very difficult disease to manage because of its chronicity and frequently relapsing nature. So it requires long term use of systemic therapy to achieve adequate disease control. Though multiple systemic therapies are available at present, unmet needs remain for safe and long term treatment.

Hence, researchers are concerned with finding new therapies for psoriasis that will be safe and efficacious.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

DEFINITION

Psoriasis is ‘a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesions consist of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and scalp. The disease is enormously variable in duration, periodicity of flares and extent. Morphological variants are common’[1].

EPIDEMIOLOGY

PREVALENCE

Psoriasis shows wide differences in prevalence among different races and in different regions of the world. It varies from 0.1% to 3% in different studies all over the world[2-4]. Influence of ethnic factors is also studied, which ranges from nil cases in somoan groups, South American Indians, aboriginal Australians to 12% in arctic Kasachye[5].

AGE OF ONSET

Even though psoriasis can occur at any age, it has bimodal age of onset where the first peak is at 15-20 years of age and second one at 55-60 years[6].

Henseler and Christophers demonstrated the existence of two distinct forms ofdisease,

Type1-- hereditary, strongly HLA associated (particularly HLA-Cw6), with an early onset (before the age of 40) and more likely to be severe and recurrent.

Type II --sporadic, late onset, HLA unrelated, without any family history and has a good prognosis.

FAMILAL OCCURENCE

Kaur et al study shows the mean age of onset of disease is 23 years in patients with family history as compared to 28 years in others.

In a German study, risk to get psoriasis was 2% if no parent or sibling was affected. It was 6% if one sibling is affected.14% and 41% if one and both the parents were affected respectively[7].

SEX RATIO

Both sexes are equally affected. But in most Indian studies, a higher prevalence has been noted in males.

ETIOLOGY

The exact etiology of Psoriasis is not known. But the following factors playa considerable role.

- **GENETIC**
- **ENVIRONMENTAL FACTORS**

ROLE OF GENETICS

- Role of genetic factors is well recognized in psoriasis.
- Danish twin study has shown the concordance rate among monozygotic twins as 64%, compared to 15% for dizygotic twins.
- Genome-wide linkage scans have revealed at least 9 chromosomal loci with significant evidence for linkage to Psoriasis (PSORS1–9)[8].
- The major Psoriasis genetic determinant is PSORS1, that accounts for 35–50% of the heritability of the disease.

- Location of PSORS1 has been identified within the major histocompatibility complex (MHC) on chromosome 6p.

- HLA associations in psoriasis- HLA-B13, HLA-B17, HLA-Cw6, HLA-DR7. HLA-B27, HLA-B38,-39, HLA-DR4 (psoriatic arthritis). Protective - HLA-B22.

ENVIRONMENTAL FACTORS

Several triggering factors have been identified, which induce or aggravate psoriasis in genetically predisposed individuals. They are as follows.

Trauma

Development of psoriasis at the site of trauma including physical, chemical, allergic, mechanical, electrical, infective, inflammatory, or surgical has been well recorded[9]. Isomorphic phenomenon (koebnerisation) at the site of sunburn, vaccination, insect/animal bite has been elicited.

Infections

Upper respiratory tract infection and tonsillitis, especially due to group A streptococci may play an important role in exacerbation of

existing psoriasis or precipitate an attack of acute guttate psoriasis in predisposed persons[10].

HIV and Psoriasis

Psoriasis and psoriatic arthropathy have been found to be associated with HIV[11]. The prognosis of acquired immune deficiency syndrome in psoriatic patients is poor. Immune dysregulation plays important role, although the exact mechanism of worsening is unclear.

Complications like arthritis, dactylitis, enthesitis are commonly encountered in HIV individuals.

Drugs

Many drugs can precipitate the onset or exacerbations of Psoriasis.

For example, lithium, beta blockers, angiotensin converting enzyme inhibitors, imiquimod, interferon-α and γ, non-steroidal anti-inflammatory drugs, anti-malarials like chloroquine and sudden withdrawal of steroids.

Seasonal variations

Winter season usually worsens the situation in psoriasis because of high humidity. Sunlight improves psoriasis but worsens it in few[12].

Hormonal factors

Psoriasis remains unaltered in 40% of pregnancies, improves in 40%, but worsens in only 14% [13]. This is due to high levels of IL-10 which is an inhibitor of type I immune response.

Precipitation of generalised pustular psoriasis during pregnancy has rarely been reported.

The facts like early age of onset in women, peak around puberty, changes during pregnancy and exacerbation of psoriasis with high dose oestrogen therapy support the view of hormonal influences.

Psychological factors

Emotional stress has been identified as a key exacerbator or trigger of psoriasis in many patients.

Exact pathogenesis is not fully understood. But increase in neuropeptides and beta-endorphin levels is believed to play the role.

Alcohol and smoking

Increased alcohol intake is a recognized stress response. Excessive drinking is a consequence of the disease and leads to treatment resistance and poor therapeutic compliance.

Patients smoking more than 15 cigarettes/day had an odds ratio of 10.5 for association with palmo-plantar pustulosis[14].

Obesity

Obese persons with psoriasis are more likely to present with severe form of disease.

PATHOGENESIS

The pathogenesis of Psoriasis is complex as multiple factors are involved. However both genetic and environmental factors are playing important role. HLA-association is invariably linked to type I plaque psoriasis and guttate psoriasis.

The characteristic features in the pathogenesis of psoriasis, include epidermal hyper-proliferation, vascular changes, inflammation and other immunological changes.

CELLULAR PARTICIPANTS

Role of T cells

The subsets of T cells, especially CD4+ and CD8+ play predominant role. Location of CD4+, CD8+ T cells is mainly seen in the epidermis and upper dermis respectively. T cells express cutaneous lymphocyte antigen (CLA) which is a ligand for E-selectin. Expression of E-selectin in skin vessels provides access to T cells to skin.

Even though both Th1&2 play the role, Th1 mediated inflammation is considered to be more important. Production of IL-23, IL-17 may play a role in chronic inflammation in psoriasis.

Natural killer- T cells

NK cells are major producers of interferon-γ and act as a bridge between innate and acquired immunity.

Killer immunoglobulin like receptors (KIRs), a regulator of NK cells can recognize HLA-C and MHC class I molecules. Association of KIR genes with psoriasis and psoriatic arthritis have been identified.

Dendritic cells (DC)

Constant communication of T cells in psoriatic lesions with several subsets of dendritic cells have been demonstrated.

1. **Langerhans cells (LC)**

Role of LC in psoriasis is still unclear. The numbers of LC are characteristically decreased in psoriasis and migration of these antigen presenting cells (APC) in response to inflammatory cytokines is also impaired in uninvolved epidermis.

2. **Inflammatory epidermal dendritic cells (IEDCs)**

Numbers of IEDCs are markedly increased in active lesions of psoriasis and other inflammatory dermatoses like eczema. But they are

almost absent in normal skin. They are differentiated from LCs by the lack of Birbeck granules and decreased expression of CD1a.

3. **Dermal dendritic cells**

While expressing no activation markers in normal skin, expression of MHC class II/factor XIIIa can be seen in active psoriatic skin lesions. A marked increase in number and maturation state of these cells noted.

4. **Plasmacytoid dendritic cells (pDCs)**

pDCs are increased in both involved and uninvolved skin in psoriasis. They link innate and adoptive immunity and produce more amount of interferon-α. Imiquimod probably acts by binding to TLR7 on pDCs and leads to exacerbation of psoriasis.

Mast cells and macrophages

Both mast cells and macrophages play prominent role in initial and developing lesions of psoriasis. Macrophages are present under the basement membrane, subjacent to proliferating keratinocytes. Expression of tumour necrosis factor-α by macrophages may play a key role.

Neutrophils

The number of neutrophils is variable although seen in upper epidermis commonly. And their role in the pathogenesis of psoriasis is unclear.

Keratinocytes

Psoriatic keratinocytes express the following,

- Pro-inflammatory cytokines
- Chemokines
- Growth factors
- Inflammatory mediators like eicosanoids.
- Innate immunity mediators like defensins, cathelicidins and S100 proteins.

Activation of regenerative maturation in psoriasis have been noted. But the mechanism by which this occurs is not known at present.

Other cells like fibroblasts and endothelial cells are also involved actively in the pathogenic process of psoriasis.

- ✓ Fibroblasts produce many chemotactic factors and help in migration of T cells out of psoriatic lesions. They also support keratinocytes proliferation in a paracrine manner.

- ✓ Endothelial cells are activated in developing as well as mature lesions of skin. Due to increase in blood flow to the lesions, influx of leukocytes and serum proteins in psoriatic lesions have been increased.

Signalling molecules in psoriasis

Cytokines and chemokines

Cytokines upregulated in psoriasis include TNF-α, IL-2,IL-6, IL-8, IL-15, IL-17, IL-18, IL-19, IL-20, IL-22.

Chemokines include CXCL9 & 10, MIP3α / CCL20, I-TAC/CXCL11.

- IL-1 induces the expression of various adhesion molecules like ICAM-1, and VCAM-1, mononuclear cell chemotaxis and also the proliferation of keratinocytes.

- IL-2 produced by CD4-T cells is indicative of T cell activation; this cytokine has not been reported in psoriatic skin.

- IL-6 is produced by keratinocytes, fibroblasts, T cells and macrophages. It stimulates keratinocytes proliferation in lesional skin. IL-6 protein levels are increased in psoriatic keratinocytes in vitro.

- IL-8 (neutrophil activating factor) is a potent chemo-attractant for neutrophils. IL-8 is produced by keratinocytes, fibroblasts, and also by lymphocytes[15].

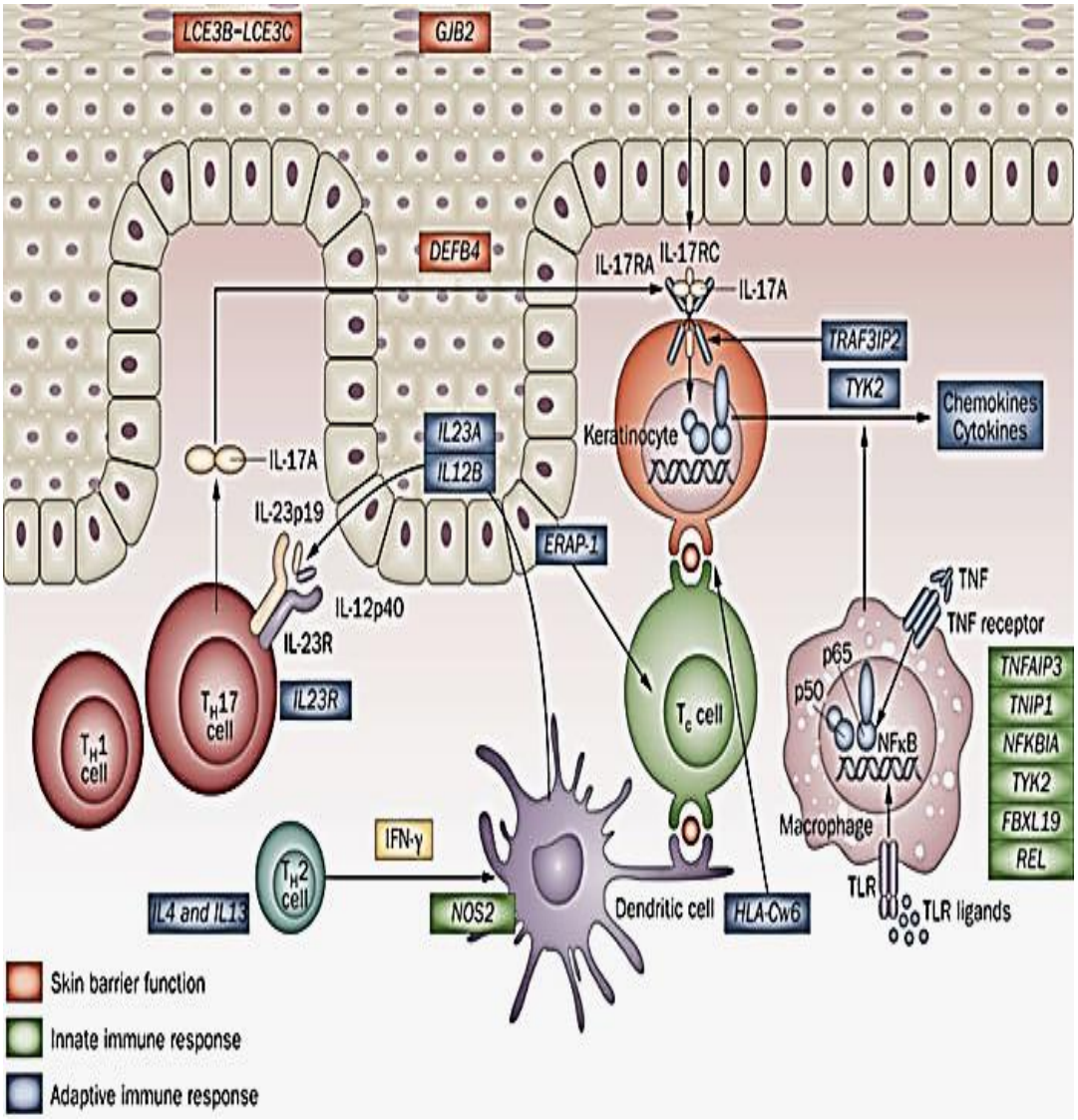
- IL-18 and IL-23 stimulate production of interferon-gamma.

- IL-23 (subset of Th17) is responsible for chronic inflammation in psoriasis.

- TNF-α is primarily localized in the dermal dendritic cells. Presence of TNF-α inducing agents like transforming growth factor-α(TGF-α), endothelial expression of adhesion molecules like ICAM-1, VCAM-1 and IL-8are all shown to be increased in psoriatic skin.

Angiogenesis is a characteristic component of psoriatic pathology and it is induced by macrophage-derived TNF-α[16,17].

PATHOGENESIS OF PSORIASIS



- INF-Gamma is produced only by activated CD4 - T cells. Lesion from involved psoriatic skin as well as serum from psoriatic patients show elevation in IFN-G. IFN-G induces macrophages to release high levels of inflammatory cytokines like TNF-α .

Innate immune mediators

- Innate immune mediators are the antimicrobial peptides, like human beta defensin-2 and cathelicidin(LL-37).

  They are increased in psoriasis in response to proinflammatory cytokines e.g,. TNF - α ,IL-1, IFN-G.

- S100A2, S100A7(psoriasin), and S100A8/A9 are overexpressed in psoriatic skin lesions which exert chemotactic and antimicrobial activity through sequestration of Zn ions.

- Complement component C5a, a potent chemoattractant for neutrophils that contribute for accumulation of the same in stratum corneum of psoriasis.

Eicosanoids

Role of eicosanoids in psoriasis is still unclear.

Levels of LTB-4, 12-hydroxyeicosatetraenoic acid and 15-hydroxyeicosatetraenoic acid are increased in lesional skin. But levels PGE and PG–F2α are increased less than two fold.

Growth factors

Following growth factors are over-expressed in psoriasis

- Members of Epidermal growth factor (EGF) family like tansforming growth factor-α (TGF-α), heparin binding EGF like growth factor, amphiregulin (ARE6).
- Keratinocyte growth factor
- Vascular endothelial growth factor (VEGF)
- Nerve growth factor (NGF)

Proteases and integrins

Levels of serine proteases and leukocyte-derived elastase are increasd in psoriasis and may contribute to stimulation of keratinocyte proliferation.

Integrinα5 and its ligand fibronectin are increased in the epidermis of psoriasis.

Signal transduction

Multiple signal transduction mechanisms like receptor tyrosine kinase, Akt, STAT, mitogen-activated protein and NF-κB pathways are all dysregulated in psoriasis.

This will affect activation of immunocytes, trafficking, and also keratinocyte responses of proliferation, differentiation and survival.

Histopathology

Changes in initial lesions

- Dermal changes like marked edema and mononuclear cell infiltrates in the upper dermis precede epidermal changes.
- Epidermal changes are mild spongiosis and focal loss of granular layer.
- Dilatation of venules in the upper dermis surrounded by minimal inflammatory infiltrates are seen[18].

Developing lesions

- There will be compact hyperkeratosis, disappearance of the granular layer and slight epidermal hyperplasia in developing lesions of psoriatic plaque.
- The lower half of the epidermis shows mitotic figures in the keratinocytes,and leukocytic infiltration in spongiotic foci.
- *Munro micro abscess* - Scattered mounds of parakeratosis, within orthokeratotic stratum corneum, appear with neutrophils.

- *Spongiform pustules of kogoj* - Neutrophils may accumulate in the malpighian layer to form this characteristic histopathological feature of psoriasis[19].

- Regular acanthosis with prominently dilated, tortuous papillary Capillaries are seen.

Changes in mature lesions

- There is parakeratosis and also focal orthokeratosis with formation of Munro microabscess.

- Spongiform pustules in the Malpighian layer, near absence of granular layer.

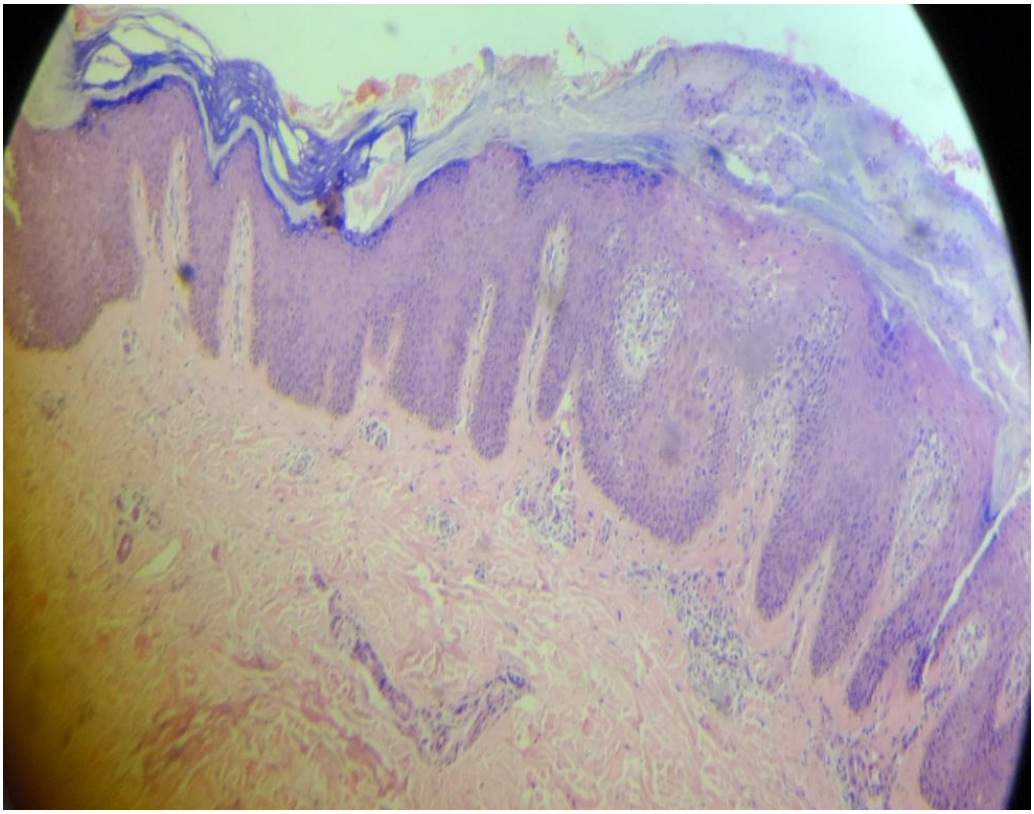
- Regular elongation of rete ridges and epidermal thinning in suprapapillary area.

- Clubbing of the rete ridges at their bases, with mononuclear leukocyte infiltrates in the lower 1/2 of the epidermis.

- Dilated and tortuous papillary blood vessels, surrounded by a mixed mononuclear and neutrophil infiltrate, and also extravasated erythrocytes[20].

HISTOPATHOLOGY

CHRONIC PLAQUE PSORIASIS



CLINICAL FEATURES

The first manifestation of psoriasis may occur at any age. The course is unpredictable as the duration of illness varies from a few weeks to whole lifetime.

Chronic stationary psoriasis (plaque type psoriasis / psoriasis vulgaris)[21-25]

Chronic plaque psoriasis is the most common form of psoriasis, accounting 90% of the patients. The plaques are well defined, reddish with silvery white scales, symmetrically distributed, localized to extensor surface of the body, like elbows, knee, lower lumbo-sacral region, buttocks, along with scalp[21].

Size of the lesion may vary from pinpoint papules to larger plaques. The successive removal of scales usually reveals an underlying glossy red membrane with small bleeding points i.e,. positive for *Auspitz's sign*. About 25% of the patients will have positive history for koebnerization which indicates active state of the disease. The plaque may sometimes be encircled by a clear peripheral halo known as *Woronoff's*ring[22].

CLINICAL VARIANTS

Guttate Psoriasis. (Eruptive psoriasis)

Gutta (latin) – ‘ a drop’

This is particularly seen in children and young adults characterized by eruption of small papules over trunk and proximal extremities (0.5-1.5 cm in size). This type of psoriasis has the strongest association to HLA-Cw6. Streptococcal infection mostly precedes or is concomitant with the onset or exacerbation of guttate psoriasis[23].

Bacterial exotoxins produced by Staph. aureus and streptococci can act as super-antigens and promote marked T-cell proliferation.

Rupioid, elephantine and ostraceous psoriasis

These terms describe plaques associated with gross hyperkeratosis.

Rupioid psoriasis-- limpet-like, cone-shaped lesions.

Elephantine psoriasis -- unusual, very persistent, thickly scaling, large plaques present over the back, hips, limbs or elsewhere[24].

Ostraceous psoriasis -- a ring-like hyper-keratotic lesion with a concave surface, resembling an oyster shell.

‘Unstable’ psoriasis

This term is employed to define the disease in which activity is marked and the course as well as outcome of the disease is unpredictable; e.g., a patient with chronic stable course of psoriasis, may suddenly become erythrodermic or pustular due to inappropriate management.

Precipitating factors for this condition are sudden withdrawal of topical/systemic corticosteroid therapy, hypocalcaemia, acute infection, overtreatment with tar/dithranol/UV irradiation, and severe emotional stress.

PUSTULAR PSORIASIS

When plaques of psoriasis is studded with superficial tiny pustules, it is called pustular psoriasis.

The classification for pustular psoriasis is as follows.

1. ***Localized pustular psoriasis*:**

The disease is confined to hands and feet, and has a chronic course.

- Palmo plantar pustulosis
- Acro dermatitis continua of Hallopeau.

2. ***Generalized pustular psoriasis:***

In this form, the whole body may get involved. The course may be acute/ subacute / even life threatening.

- Acute(Von Zumbusch)
- Of pregnancy(Impetigo herpetiformis)
- Infantile and juvenile
- Circinate
- Localized (not hands and feet).

Erythrodermic psoriasis

Two forms exist. In the first form, chronic lesions may progress gradually into an exfoliative phase to involve the whole cutaneous surface. There are usually some areas of uninvolved skin. The characteristics of psoriasis are retained well, mild treatment is generally well –tolerated and this form has a better prognosis.

The second form is part of the spectrum of 'unstable' psoriasis. It may occur at any time, presenting suddenly, due to increasing intolerance to local applications, UV therapy and of loss of control over the disease. It is more frequent in psoriatic arthropathy. Itching is often severe in contrast to stable form.

Classification based on site

Scalp

Lesions in the scalp are characterized by very thick plaque involving the occiput or diffuse plaque affecting the entire scalp.

A non-specific reaction pattern known as pityriasis (tinea) amiantacea is commonly seen in children. It is characterised clinically by asbestos like, firmly adherent scales to scalp. Hair loss is not common[25].

Penis

In uncircumcised male patients, psoriasis may present as solitary, well defined non-scaly plaque on the glans. In such cases it should be differentiated from Erythroplasia of Queyrat or Zoon's plasma cell balanitis.

Flexural (inverse) psoriasis

Psoriasis involve the axilla, submammary folds, groin, vulva, and gluteal cleft is more commonly seen in adults. The scales are reduced or absent with a glazed hue surface and fissuring.

It will be particularly difficult to differentiate from infective dermatitis and seborrhoeic dermatitis.

Hands and feet

It may present as well to ill defined hyperkeratotic scaly plaques involving the palms and soles. Eczema should be considered as a close differential diagnosis in particular.

NAIL CHANGES IN PSORIASIS

Nail changes can be seen in up to 40% of patients in psoriasis [26].

Nail involvement may be severe in case where psoriasis has early onset and familial. All types of nail involvement may occur in psoriatic arthritis.

Nail segment involved		clinical sign
1. Proximal matrix	=>	pitting, Beau's line, onychorrehexis
2. Intermediate matrix	=>	leukonychia
3. Distal matrix	=>	nail plate thinning, focal onycholysis, erythema of lunula
4. Nail plate	=>	crumbling and destruction
5. Nail bed	=>	onycholysis, splinter hemorrhages, Salmon patch
6. Hyponychium	=>	onycholysis, subungual hyperkeratosis

ATYPICAL FORMS

Linear and zonal lesions

Linear lesions along with typical psoriatic plaques may present as part of koebner phenomenon. True linear psoriasis is extremely rare.

Zonal lesions representing koebner reaction at a site of herpes zoster have been described.

Seborrheic psoriasis

Patients present with reddish plaques with greasy scales localised to seborrhoeic areas (the scalp, glabella, nasolabial folds, presternal areas, and flexures) may be a common clinical finding. In most of the situation, differentiating it from seborrhoeic dermatitis will be hard.

Mucosal lesions

Oral mucosae

- Grey, white or translucent plaques, diffuse reddish areas or annular forms and geographic tongue have been described.
- But true mucosal involvement is rare in psoriasis.

- **Geographic tongue (Benign migratory glossitis / glossitis areata migrans)**

  -An idiopathic inflammatory condition characterised by focal loss of filiform papillae.

  -Presents as asymptomatic reddish patches with serpiginous borders, resembling a map.

  -Migratory in nature

  -Association of geographic tongue with HLA Cw6 have been identified.[28-31].

Ocular involvement

- Blepharitis, xerosis, conjunctivitis, keratitis, symblepheron and uveitis have been reported in psoriasis[32].

- Patients with pustular psoriasis or psoriatic arthritis and who were on methotrexate have been shown to have features of uveitis.

PSORIATIC ARTHRITIS[33,34]

- Psoriatic arthritis is an inflammatory arthritis that is seen in 5%-10% of patients with psoriasis.
- It is a sero-negative arthritis. i.e., negative for rheumatoid factor.
- Associated with HLA –B 27, B-38, A-26.

The Moll and Wright classification[35]includes following types

1. Classic psoriatic arthritis involving the distal inter-phalangeal joints.
2. Oligo-articular arthritis.
3. Rheumatoid type of psoriatic arthritis (symmetric polyarthritis).
4. Arthritis mutilans.
5. Psoriatic spondylitis with or without sacroiliitis

DISEASES ASSOCIATED WITH PSORIASIS

Following diseases have been reported to have association with psoriasis-

They are

- *Cutaneous disorders*-- vitiligo,bullous pemphigoid, atopic dermatitis, infections (bacterial, viral, fungal), non-melanoma skin cancers[36,37].

- *Systemic disorders*-- Crohn'sdisease[38], gout[39], chronic recurrent multifocal osteomyelitis[40], SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis)[41].

COMPLICATIONS

- Infections -- folliculitis and furunculosis rarely due to staph. aureus[42].

- Itching -- more common in unstable form.

- Erythrodermic psoriasis.

- Psoriatic arthritis.

- Nephritis and renal failure – mesangio capillary glomerulo-nephritis, acute tubular necrosis have been reported[43,44].

- Hepatic failure -- pustular / erythrodermic psoriasis, or due to drugs, oligaemia, alcoholism.

- Apical pulmonary fibrosis -- non articular complication of ankylosing spondylitis.

- Secondary amyloidosis.

DIFFERENTIAL DIAGNOSIS

1. **Psoriasis vulgaris** :-

Most likely- nummular eczema, cutaneous T-cell lymphoma (CTCL), tinea corporis

To rule out- Bowens disease, paget's disease (extra-mammary)

Consider - seborrhoeic dermatitis, pityriasis rubra pilaris (PRP), hypertrophic LP, Erythro keratoderma, subacute cutaneous lupus erythematosus.

2. **Erythrodermic :-**

Most likely - eczema, CTCL, PRP.

3. **Pustular :-**

Most likely - impetigo, reactive arthritis syndrome, candidiasis.

Consider- pemphigus foliaceus, IgA pemphigus, subcorneal pustular dermatosis, acute generalised exanthematous pustulosis.

4. **Guttate :-**

Most likely - lichen planus, pityriasis rosea, pityriasis lichenoides chronica.

To rule out - secondary syphilis.

Consider - parapsoriasis (small plaque), drug eruption.

INVESTIGATIONS

For initiation of treatment, following investigations should be done.

1. **Complete blood count** –including platelet count.
2. **Serum calcium.**
3. **Serum uric acid.**
4. **Renal function test**- BUN, blood urea, serum creatinine.
5. **Blood sugar level**.
6. **Liver function tests**- including liver enzymes and protein levels.
7. **Fasting lipid profile**- Total Cholesterol, Triglycerides, HDL-C, LDL-C.
8. **Urine routine** – Albumin, Sugar and Deposits.
9. **Screening** - for HIV, HEP B & C and mantoux test.
10. **Cardiac evaluation**- ECG
11. **Radiological evaluation** - Chest X-Ray, X-Ray Joints.
12. **Ultrasonogram**- abdomen.
13. **Urine pregnancy test**.
14. **Skin biopsy**

CLINICAL SEVERITY ASSESMENT IN PSORIASIS

Many tools can be used for the assessment of psoriasis clinically. They are as follows

1. BSA - Body Surface Area.
2. PASI - Psoriasis Area and Severity Index.
3. SAPASI - Self Administered Psoriasis Area And Severity Index.
4. NAPASI - Nail Psoriasis Severity Index .
5. CASPAR - Scoring of psoriatic arthritis .

Among these, PASI is the most commonly used one.

BODY SURFACE AREA (BSA)

It is the simplest scoring system which follows the rule of nine as in case of burns. It just reflects surface area of the body involved but not the severity of the disease.

PSORIASIS AREA AND SEVERITY INDEX (PASI)[45]

PASI is a useful tool in monitoring the response of psoriasis to any therapeutic regimen.

Four sites are separately scored. They are head (h), upper limbs (u), trunk (t) and lower limbs (l).

Morphological evaluation done by three parameters namely, erythema (E), induration (I) and scaling (S).

They are graded on a severity scale of 0 to 4.

0 = nil, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

The addition of these scores for each site is multiplied by the grading for area wise percentage involvement of that particular site in following manner

1 = < 10% area involved, 2 = 10% to 29%, 3 = 30% to 49%

4 = 50% to 69%, 5 = 70% to 89%, 6 = > 90%

Four body regions represent about 10%, 20%, 30% and 40% of the body surface area respectively, they are given corresponding score of 0.1, 0.2, 0.3 and 0.4.

The score vary from 0 to 72 in steps of 0.1.

The main limitation of this scoring system is inter-observer variation. This necessitates scoring by the same evaluator.

	AREA (A)	**ERYTHEMA (E)**	**INDURATION (I)**	**SCALING (S)**
HEAD(h)				
UPPER EXTREMITY(u)				
TRUNK(t)				
LOWER EXTREMITY(l)				
TOTAL				

$$PASI=0.1(E_h+I_h+S_h)A_h+ 0.2(E_u+I_u+S_u)A_u+0.3(E_t+I_t+S_t)A_t+0.4(E_l+I_l+S_l+)A_{l.}$$

Nail Psoriasis Severity Index (NAPASI)

NAPASI is used to evaluate nail psoriasis. Here the nail is divided into 4 quadrants by imaginary horizontal and longitudinal lines and assessed in each quadrant for:

- ✓ Psoriasis of nail matrix: pitting, leukonychia, red spots in lunula and crumbling of nail plate.
- ✓ Psoriasis of nail bed: oil drop sign, onycholysis, splinter hemorrhage, sub-ungual hyperkeratosis, nail discoloration.

NAPASI Scoring

Score	**Lesions**
0	If findings are absent.
1	If present in 1 quadrant of nail.
2	If present in 2 quadrants of nail.
3	If present in 3 quadrants of nail.
4	If present in 4 quadrants of nail.

Nail score is obtained by the summation of nail matrix and nail bed scores (0-4 each) NAPSI is obtained by adding the total score of all involved nails.

CASPAR (Classification Criteria for Psoriatic Arthritis)

- Current psoriasis (assigned a score of 2)
- A history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
- A family history of psoriasis (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
- Dactylitis (assigned a score of 1)
- Juxta-articular new bone formation (assigned a score of 1)
- RF negativity (assigned a score of 1)
- Nail dystrophy (assigned a score of 1)

TREATMENT

Following treatment options available,

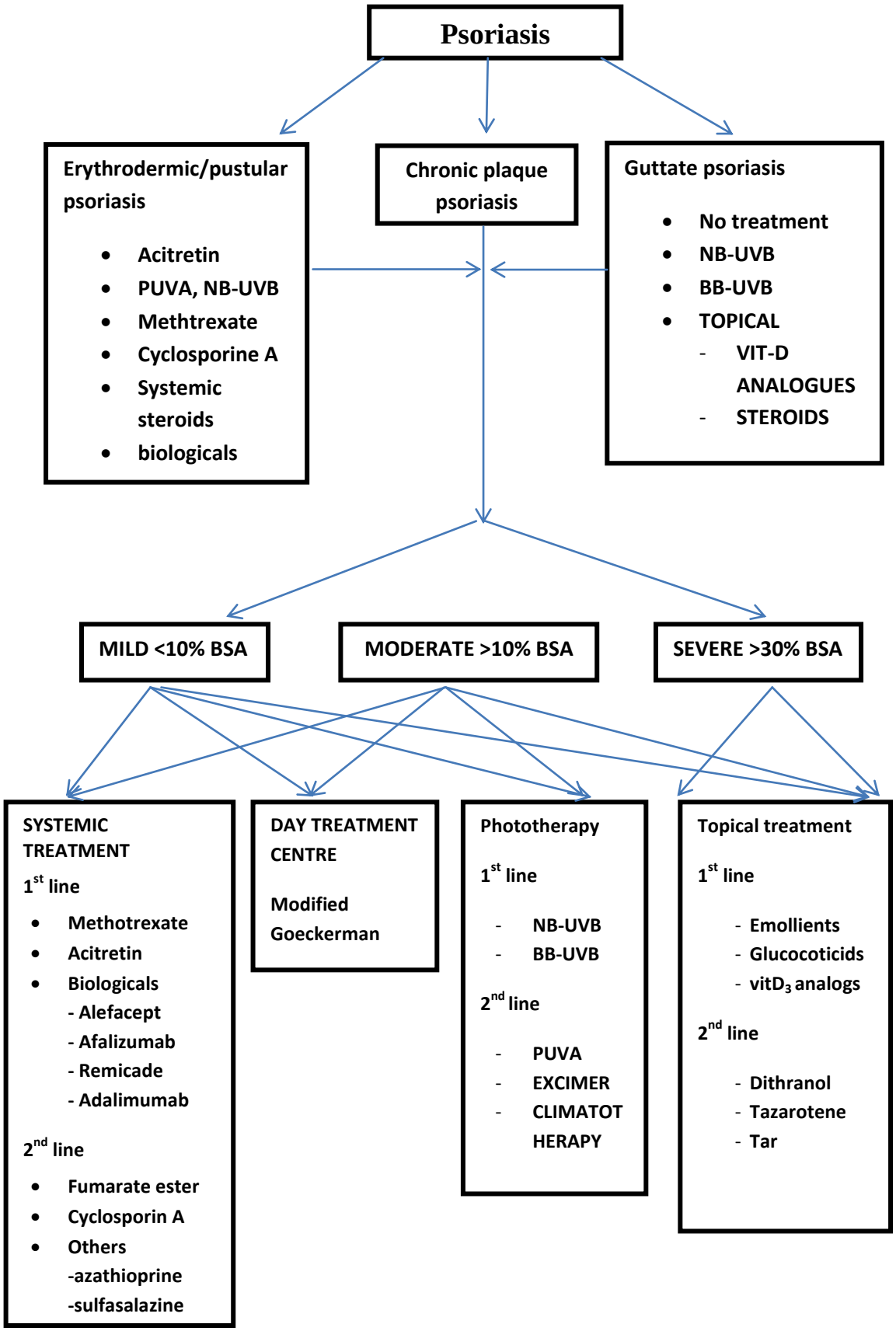
1. TOPICAL : Emollients, Keratolytics, Tar, Anthralin, Vitamin D analogues, Vitamin A analogues (retinoids), Calcineurin inhibitor, Corticosteroids.

2. PHOTOTHERAPY : PUVA, NB-UVB.

3. SYSTEMIC: Methotrexate, Cyclosporine A, Retinoids, Hydroxyurea, Systemic steroids, Fumaric acid esters, Mycophenolate mofetil, Biological agents.

4. MISCELLANEOUS: 6-thioguanine, Azathioprine, Sulfasalazine, protein kinase C inhibitors, Tacrolimus, Pimecrolimus, Zidovudine, Liarozole, Somatostatin, Photodynamic therapy, Lasers-excimer (308nm).

ALGORITHM FOR TREATMENT OF PSORIASIS



METHOTREXATE (MTX)

Methotrexate, a potent folic acid antagonist, acts by inhibiting the enzyme dihydrofolate reductase. Initially approved for the treatment of psoriasis by USFDA and now used widely in various dermatological condition[46].

MECHANISM OF ACTION

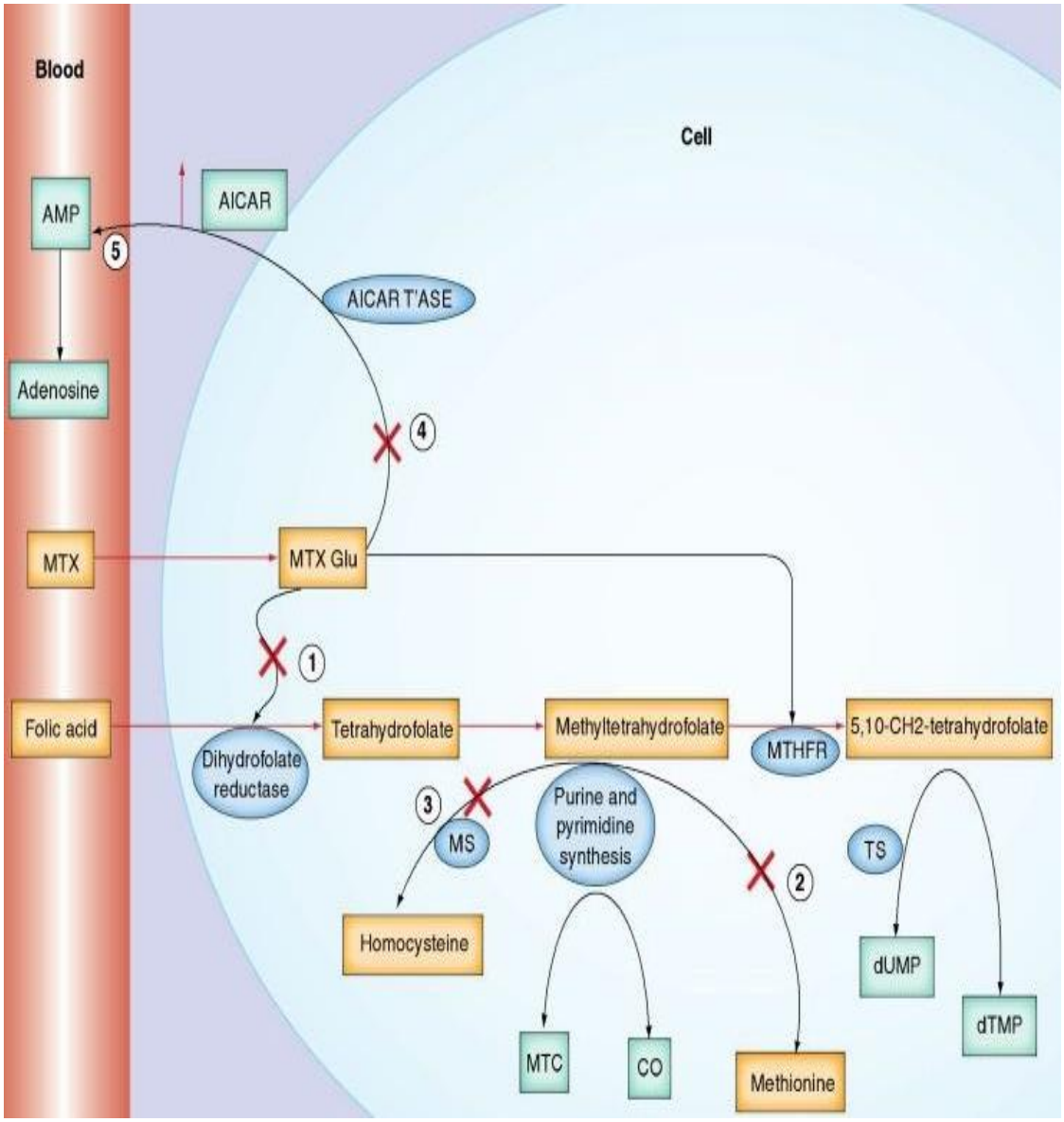
MTX is a folic acid analog which acts as a competitive inhibitor for folate receptors. It enters cells either through an active transport mechanism or by facilitated diffusion. Active metabolites of MTX (polyglutamated forms) are potent inhibitors of DHFR and also play a key role in toxicity[47].

DNA SYNTHESIS EFFECTS

Methotrexate causes inhibition of cell division, which is specific for S-phase of the normal cell cycle. i.e., DNA synthesis.

Methotrexate competitively and reversibly inhibits dihydrofolate reductase enzyme with an affinity greater than that of folic acid. This prevents the conversion of dihydrofolate to tetrahydrofolate. Tetrahydrofolate [THF] is a cofactor in production of 1-carbon units, therefore needed for DNA and RNA synthesis. Other than DHFR, thymidylate synthase is also inhibited by MTX.

MECHANISM OF ACTION- METHOTREXATE



EFFECTS ON T & B CELLS

Methotrexate not only affects the lymphocytes proliferation, but also inhibits migration of activated T cells. It depresses cutaneous lymphocyte associated antigen positive T cells and E-selectin of endothelial cells.

Though MTX can suppress both primary and secondary antibody responses, no significant effect on delayed type hypersensitivity has been noted.

ANTI-INFLAMMATORY EFFECTS

Anti-inflammatory effect of methotrexate is because of its inhibitory action on folate dependent enzyme i.e,.5-aminoimidazole carboxamide ribonucleoside transformylase (AICART).

This will lead to accumulation of AICAR and release of adenosine. With potent anti-inflammatory effects, adenosine inhibits secretion of pro-inflammatory cytokines like IL-6,-8, TNF-α, INF-γ and also retards function of polymorphonuclear lymphocytes. Modulation of intercellular adhesion molecule-1 (ICAM-1) has also been noted.

PHARMACOKINETICS

Methotrexate can be given orally, subcutaneously, intramuscularly and also intravenously. It is rapidly absorbed orally, although absorption may be variable with higher doses. Plasma peak level reaches slowly after an hour of ingestion. In some cases intrathecal injection of drug is needed as its penetration of blood brain barrier is poor.

Once absorbed, methotrexate undergoes a triphasic reduction in plasma. In first phase (3/4thof an hour),distribution of the drug occurs throughout the body.

In 2nd phase, plasma level is reduced over 2-4 hours due to excretion of the drug via kidney. Methotrexate being a weak organic acid, its predominant mode of excretion is through the kidneys.

During 3rd phase, methotrexate is released slowly from the tissues as it is primarily bound to dihidrofolate reductase. The terminal half-life therefore varies between 10-27 hours.

Methotrexate is primarily available as 2.5mg tablet but recently 5, 7.5, 10 and 15 mg tablets are also available in the market. Injectable

form is available as solution for intravenous, intramuscular, intrathecal, and subcutaneous administration (2-ml vials with 2.5 to 25mg/ml).

INDICATIONS [48]

FDA-approved dermatologic indications

- Psoriasis, Sezary syndrome

Off - label dermatological uses

- **Proliferative dermatoses-**Reiter's disease, Pityriasis lichenoides et varioliformis acuta**,** Pityriasis rubra pilaris.
- **Immunobullous diseases**-Pemphigus vulgaris, cicatrical pemphigoid, Epidermolysis bullosa aquisita, Bullous pemphigoid.
- **Vasculitis and neutrophilicdermatoses** –Pyoderma gangrenosum ,Leucocytoclastic vasculitis, Cutaneous polyarteritis nodosa, Behcets disease, Kawasaki disease.
- **Connective tissue disorders -** Morphea / localized scleroderma, subacute cutaneous lupus erythematosus, systemic lupus erythematosus, Dermatomyositis, Systemic scleroderma.
- **Dermatitis**- Atopic dermatitis

- **Other dermatoses**

  Kertoacanthoma, Sarcoidosis, Keloids, mycosis fungoides, Lymphomatoid papulosis, Cutaneous crohn's disease, Chronic idiopathic urticaria.

Contraindications

Absolute

Pregnancy and lactation

Relative

Unreliable patients, renal and hepatic diseases metabolic diseases like diabetes mellitus, severe hematological abnormalities, men or women contemplating conception, any active infections (eg., TB), immunodeficiency syndromes.

Adverse effects

- **Hepatotoxicity** – the risk of methotrexate induced cirrhosis varies from 0 – 25% in various reports. The risk of liver damage can be reduced when the cumulative dose is below 1.5g.Patients with cumulative dose of 4.0 g or above are particularly at risk for developing cirrhosis and liver fibrosis.

Intake of alcohol and other hepatotoxic drugs will further aggravate the toxicity.

- **Pulmonary toxicity** – acute pneumonitis, a rare life threatening complication have been reported in patients who received small doses of MTX. Pulmonary fibrosis develops more gradually in long term patients.

- **Haematological abnormalities** – methotrexate can cause pancytopenia which can endanger patient's life. Routine folic acid supplementation will reduce the risk of pancytopenia.

  Concurrent use of sulphonamides and NSAIDs will further aggravate the risk of toxicity. Leucovorin (folinic acid) should be promptly used in case of acute toxicity.

- **Malignancy induction** – use of methotrexate in collagen vascular diseases is associated with lymphoma but it is rarely reported in patients with psoriasis.

- **Gastrointestinal effects**

  Most commonly reported adverse effects are nausea and anorexia whereas, diarrhoea and ulcerative stomatitis are less frequently noted.

- **Reproductive effects**

  Methotrexate is a potent abortifacient and teratogen, but shows very less mutagenic and carcinogenic potential when compared with alkylating agents. Women of child bearing age who take methotrexate must use reliable birth control measures. It can also cause reversible oligospermia in men.

- **Renal effects**

  High dose (i.e., 50-250mg/m^2 intravenously) methotrexate therapy may lead to renal toxicity due to precipitation of methotrexate in renal tubules.

- **Other adverse effects**

  Headache, fatigue, alopecia, phototoxicity, papular eruption, acral erythema, toxic epidermal necrosis, cutaneous ulceration, vasculitis, osteopathy and rarely stress fractures.

MONITORING

Before starting the drug careful history taking and physical examination should be done.

LABORATORY

- Complete blood count including platelet count.
- Liver function test.
- Renal function test.(including BUN)
- Screening for HIV, hepatitis B&C.
- Urine pregnancy test.
- Chest x ray and mantoux test.

Guidelines to follow up are

- CBC including platelet count and LFT- 5-6 days after test dose. Every 1-2 wks for 2-4 wks. Gradually decrease to every 3-4 months.

- Renal function test- once or twice yearly.

- Liver biopsy- should be done for low risk patients after every 1.5-2.0 g total dose. For high risk patients every 1.0 g of total dose.

AZATHIOPRINE

Azathioprine, a purine analog, was introduced in 1961 for renal transplantation as an immunosuppressant.

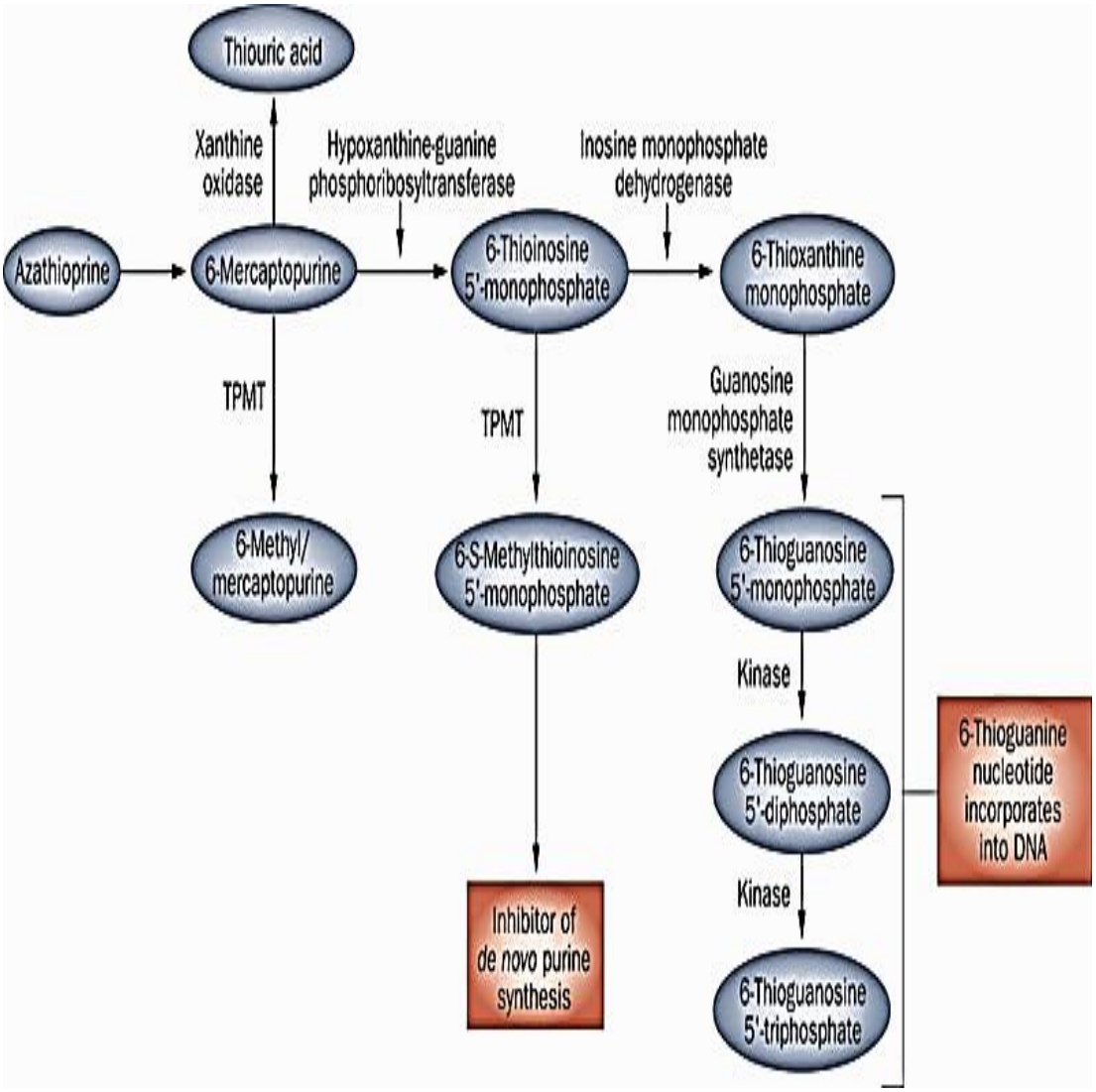
In dermatology it is used as a steroid sparing agent, therefore allowing to decrease the dose of systemic steroids or can be used as monotherapy. It is less toxic than its parent component 6-mercaptopurine (6-MP)[49].

MECHANISM OF ACTION

Conversion of azathioprine to 6-MP initially, followed by anabolization to its active form 6-thioguanine (6-TG), by the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) occurs following absorption. 6-TG is similar structurally to purine adenine and guanine, so that is incorporated into DNA and RNA inhibiting purine metabolism and cell division[50].

Both T and B cell mediated functions are depressed. Diminished B cell function results in decreased antibody production, which is of central importance in its usage in immunobullous disorders[51].

MECHANISM OF ACTION- AZATHIOPRINE



Number and functioning of Langerhans cells and other antigen presenting cells in the skin are decreased. This will further enhance the immuno-suppressive effects of the drug.

Other than the active component (6-TG) of the drug, two inactive metabolites are produced by the enzymes Xanthine oxidase and thiopurine methyl transferase (TPMT)[52].

PHARMACOKINETICS

Azathioprine is well absorbed orally (88%). It reaches peak plasma levels in less than 2 hrs with half- life around 5 hrs.

The drug is completely metabolized and its active metabolite 6-TG accumulates in tissues to provide maximal clinical benefits around 8-12 wks.

It can easily cross the placenta, but not the blood brain barrier.

Dosage is 1-3 mg/kg/day. Available in 25,50,75,100-mg tablets.

An injectable formulation is also available (100 mg vial).

INDICATION

FDA-APPROVED

- Organ transplantation.
- Severe rheumatoid arthritis

(none specific to dermatology)

OFF-LABEL DERMATOLOGIC USE

- **Immuno-bullous dermatoses -** Bullous pemphigoid, pemphigus vulgaris, cicatrical pemphigoid.
- **Neutrophilic dermatoses -** Behcet's syndrome, pyoderma gangrenosum.
- **Connective tissue disorders -** SLE, DLE, relapsing polychondritis, dermatomyositis.
- **Dermatitis and papulosqaumous diseases-** contact dermatitis. Atopic dermatitis, psoriasis, lichen planus.
- **Vasculitis –** polyarteritis nodosa, wegener's granulomatosis.

- **Photodermatoses -** actinic dermatitis, PLE, persistent light reaction.

- **Others -** erythema multiforme, sarcoidosis, chronic GVHD.

CONTRAINDICATIONS

Absolute- pregnancy, hypersensitivity to drug, any active infections.

Relative- use of allopurinol, prior use of alkylating agent.

ADVERSE REACTIONS

- **Myelosuppression -** neutropenia, agranulopenia and pancytopenia.

- **Infections -** herpes simplex, HPV, scabies.

- **GIT -** gastritis, pancreatitis.

- **Hepatic -** transient elevation in enzymes level, rarely hepatotoxicity.

- **Teratogenicity -** congenital malformations like polydactyly, myelo-meningocele, talipus equino varus.

- **Malignancies -** lymphoma and cutaneous SCC.

- **Hypersensitivity syndrome -** cutaneous eruptions varies from morbilliform to erythema nodosum like.

MONITORING

Before starting the drug, complete clinical evaluation to focus on skin and lymphoreticular system should be done.

History of use of allopurinol or any alkylating agents has to be elicited.

LABORATORY

- Urine pregnancy test.
- Complete blood count including platelet count.
- Liver and renal function tests.
- Mantoux test, chest x ray.
- Urine analysis.
- Screening for HIV.

SPECIAL TEST

Dose modification should be done according to TPMT assay[53], before initiation of AZT,

- If TPMT level < 5.0 U = no treatment with azathioprine.
- TPMT > 5.0 U but < 13.7 U = 0.5 mg/kg maximum daily dose.
- TPMT > 13.7 U but < 19.0 U = 1.5 mg/kg maximum daily dose.
- TPMT > 19.0 U = 2.5 mg/kg maximum daily dose.

  No need to repeat the TPMT assay following baseline determination closely.

Guidelines to follow up are

- Complete blood count including platelet count.
- Liver function test including AST & ALT.

Tests should be done biweekly for the first 2 months, every 2-3 months thereafter[54].

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

1. **To compare the EFFICACY, SAFETY and TOLERABILITY of ORAL METHOTREXATE 15mg/week Versus ORAL AZATHIOPRINE 50mg/day in chronic plaque psoriasis.**

2. **To look for adverse effects during and after the treatment**

METHODS AND MATERIALS

METHODS AND MATERIALS

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL, CHENNAI.

TYPE OF STUDY : RANDOMISED, PROSPECTIVE, OPEN LABEL, PARALLEL GROUP COMPARATIVE STUDY.

TIME DURATION : One year.(June 2013 to May 2014)

SAMPLE SIZE : 2 groups, each containing 20 patients.

STUDY PROCEDURE

This study was conducted in accordance with the ethical committee approval obtained on June 2013 (Annexure 3)

A brief and relevant medical history with physical examination will be taken at screening visit to ensure all the relevant eligibility criteria are met.(Annexure 1).

Informed and written consent was obtained(Annexure 2).

After successful screening, patient would be randomised to one of the two treatment groups as follows,

GROUP A(n=20) : Patients who fulfil inclusion criteria and willing to take part in trial and sign consent letter would be included in the study. They would be administered T.METHOTREXATE 15mg/week for 12 weeks. Efficacy will be assessed by monitoring PASI score every week. Safety and tolerability monitored by clinical examination with complete haemogram weekly and liver function test biweekly.

GROUP B(n=20) **:** Patients who fulfil inclusion criteria and willing to take part in trial and sign consent letter would be included in the study. They would be administered T.AZATHIOPRINE50mg/day for 12 weeks. Efficacy will be assessed by monitoring PASI score every week. Safety and tolerability monitored by complete haemogram and liver function tests biweekly.

In both the groups, adjuvant treatment with topical emollients like liquid paraffin was allowed.

Endpoints and Assessments

The primary endpoint was achieving PASI 75 at week 12. Patients in both the groups who had achieved PASI 75 and PASI 50 at week 12

were then followed up for a period of 12 weeks, to look for any adverse effects and decrease in efficacy.

Thus, all patients were assessed at screening, at baseline, and every weeks thereafter. Safety of both the drug regimens was evaluated by the incidence of adverse effects (CTC version 2.0)[55]and changes in laboratory parameters.

Inclusion criteria:

1) Male
2) Female

} Chronic plaque type- Psoriasis

3) Age >18 years
4) PASI >10
5) Investigations within normal limits.
6) Patients willing for trial and follow up.

Exclusion criteria:

1) Pregnant and lactating woman.

2) Patients who received oral or parenteral treatment for Psoriasis vulgaris during the 4 weeks before trial or topical treatment during the week before trial.

3) Other clinical type of psoriasis like erythroderma, pustular psoriasis that would interfere with study evaluation.

4) Active Bacterial or viral skin infections.

5) Patients on any other immunosuppressant drugs.

6) HIV Patients.

7) H/o active TB / old case TB.

8) H/o Cardiac disease.

9) H/o liver disease and

10) H/o renal disorder.

Investigations:

- Complete haemogram including platelet count.
- Liver function test.
- Renal function test.
- Blood glucose level.
- Serum calcium and uric acid.
- HIV and VDRL screening
- Hepatitis B & C
- Mantoux test
- Chest x-ray, ECG
- Ultrasound Abdomen and pelvis
- ENT & dental opinion to r/o focal sepsis
- Skin biopsy.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

This study was started in June 2013 and completed in May 2014 when the last patient completed his follow up. A total of 40 patients were enrolled in the study who were randomised to either of the two treatment groups. All the 40 patients in both groups received the specific dose of medication and completed 24 weeks of the study period.

Patient demographics and baseline disease characteristics were generally well balanced across both the treatment groups. Youngest age of the patient in this study was 23 years and oldest was 64 years. The mean age was 42 years. The highest score of PASI was 21.8 and lowest was 12.3.Mean PASI score at baseline was 16.1.The mean duration of Psoriasis at baseline was 5 years.

In the Methotrexate and Azathioprine groups, respectively, 17(85%) and 16(80%) had received prior systemic therapy or phototherapy.

13(65%) patients in the Methotrexate group and 14 patients in the Azathioprine group (70%) had nail involvement in the form of pitting, nail dystrophy, beau's lines and / or subungual hyperkeratosis.

Total number of patients in the study: 40

Study population

This study included 40 patients ; 33 male and 7 female patients.

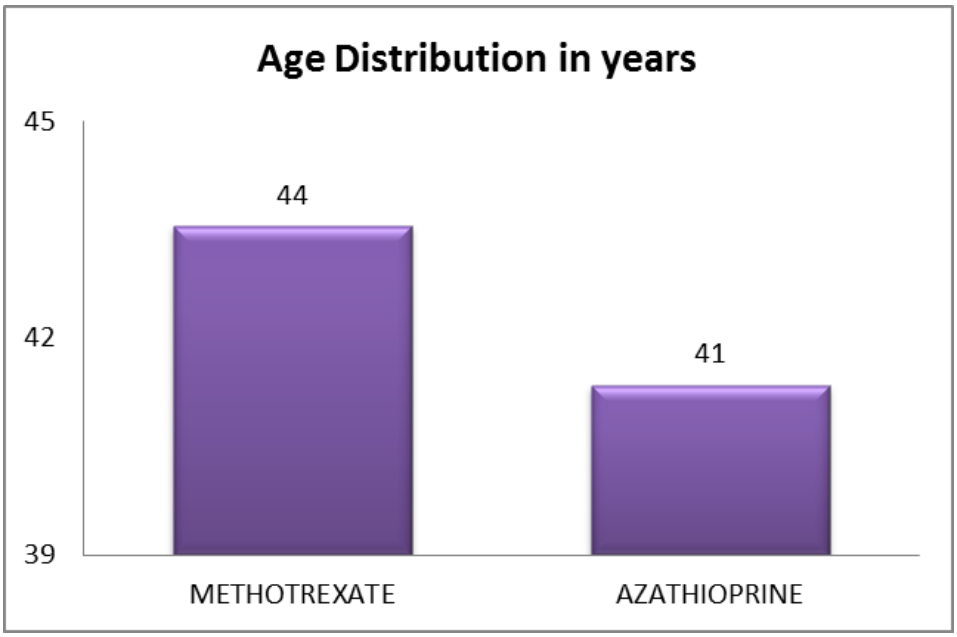
Youngest patient was 23 years of age and oldest was 64 years of age. All the patients fulfilled the inclusion and exclusion criteria.

Table 1 – Age wise distribution of study population

Age group (years)	No. of patients
20 – 40	**18**
41 – 60	**19**
61 – 80	**3**

The collected data was analysed and data descriptive statistics frequency analysis, mean, S.D, percentage analysis were used to describe it. Independent t-test was used to find the difference between bivariate samples. Chi-square test was used for categorical values. Probability value (**P= .05**) is considered as significant in all above statistical stools.

Chart 1 : Mean Age of study population



The mean age of study population was 42. The mean age in methotrexate group was 44 and azathioprine group was 41.

Table 2: Sex wise distribution of study group

Drug	Male	Female	Total
Methotrexate	16	4	20
Azathioprine	17	3	20

Chart 2: Sex wise distribution of study cases

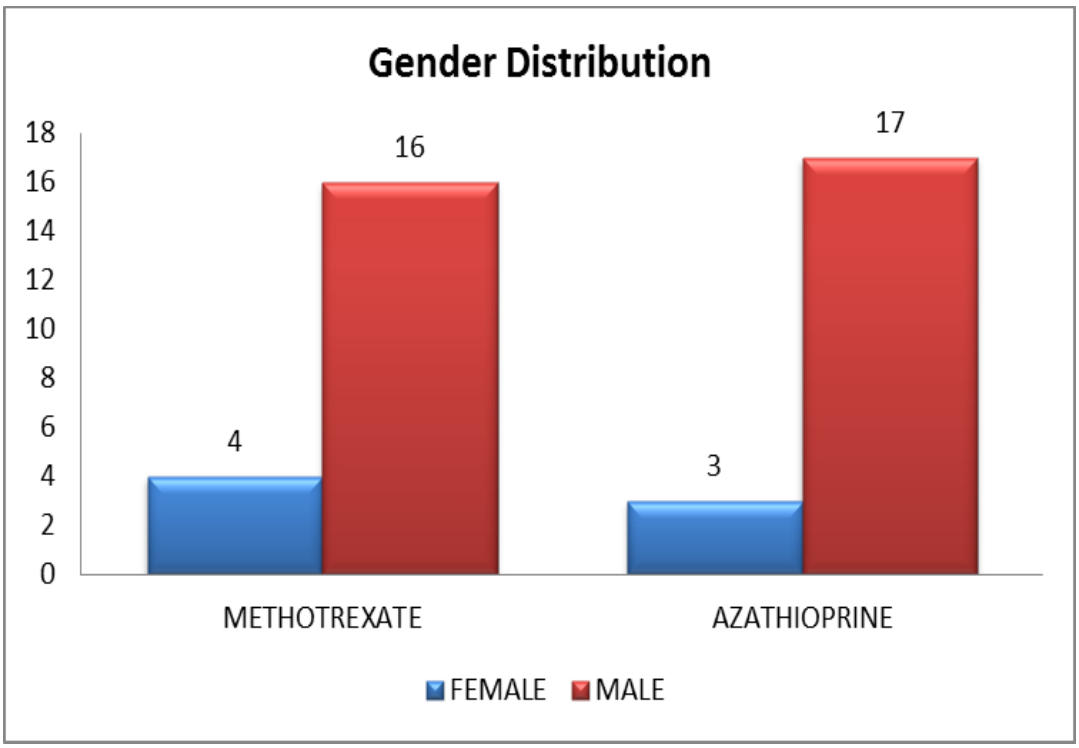
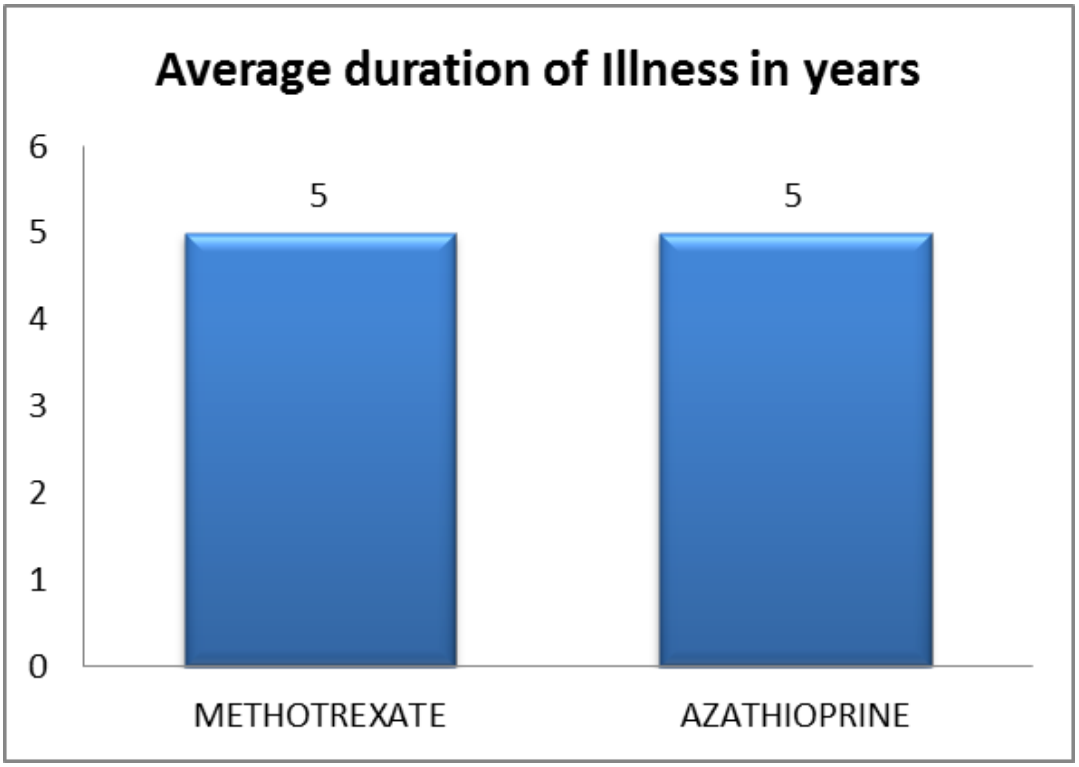


Chart 3 : Mean duration of illness in both groups



Mean duration of the disease in both groups were 5 years.

EFFICACY

At week 12 PASI 75 response was achieved by 14 patients in Methotrexate group and 5 patients in Azathioprine group (70% vs 25%; **p=0.036**). Similarly PASI 50 response was achieved by 6 patients in Methotrexate group and 13 patients in Azathioprine (30% vs 65%). 2 patients in Azathioprine group achieved PASI 25 at week 12 (10%).

In the Methotrexate group mean PASI decreased from 16.2 at baseline to 4.2 at 12 week (74%). And in Azathioprine group it was from 15.3 to 5.6 (62.1%)

The mean duration of remission in Methotrexate group was 2 months and in Azathioprine group it was 1 month.

Table 3 : Week wise reduction in Mean PASI score

Duration	Methotrexate	Azathioprine
Baseline	16.2	15.3
4 weeks	12.6	12.9
8 weeks	7.7	8.5
12 weeks	4.2	5.6

This table shows weekly reduction in Mean PASI score from the baseline. In the Methotrexate group mean PASI decreased from 16.2 at baseline to 4.2 at 12 weeks (74%). And in Azathioprine group it was from 15.3 to 5.6 (62.1%)

Chart 4 : Week wise reduction in PASI

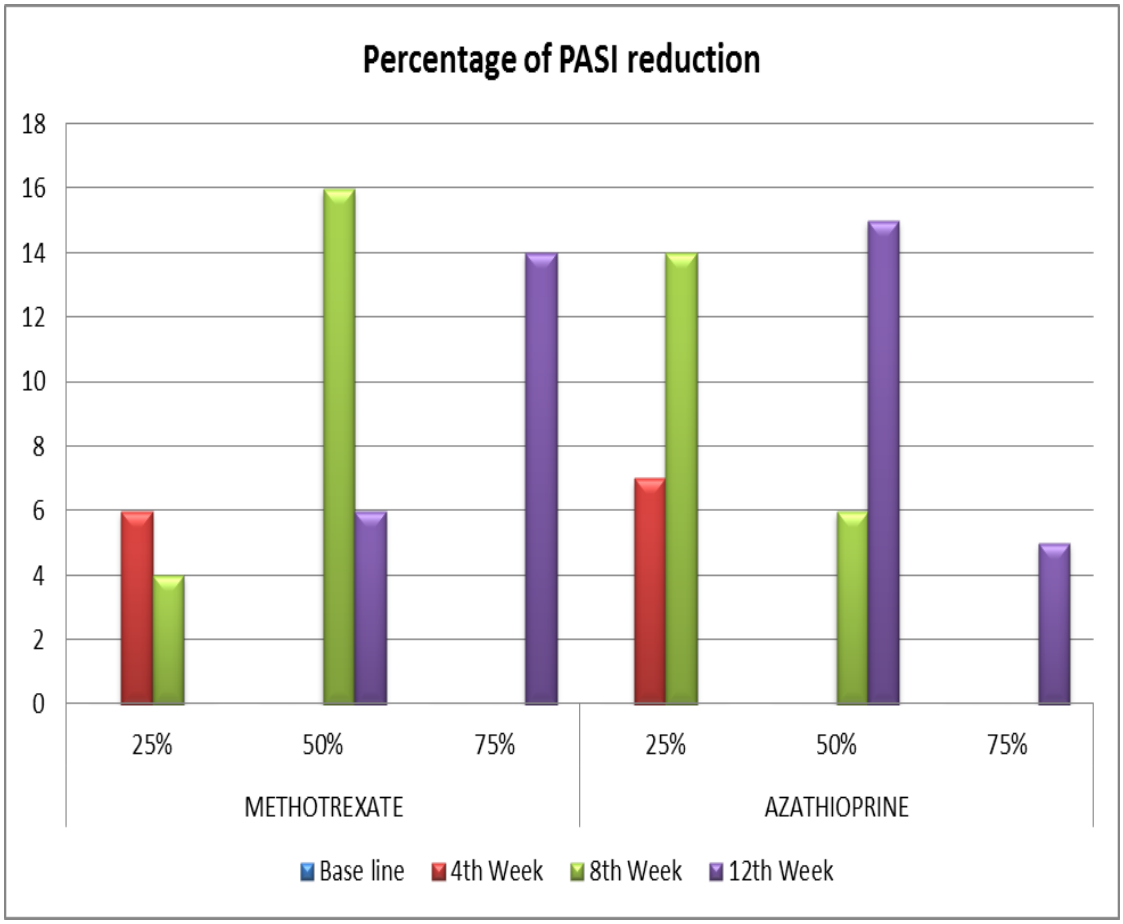


Table 4 : Week wise reduction in PASI score – Methotrexate

Week	25%	50%	75%
Week 4	6	0	0
Week 8	4	16	0
Week 12	0	6	14

Table 5 : Week wise reduction in PASI score – Azathioprine

Week	25%	50%	75%
Week 4	7	0	0
Week 8	14	6	0
Week 12	0	15	5

Chart 5 : Percentage reduction in PASI – 4th week

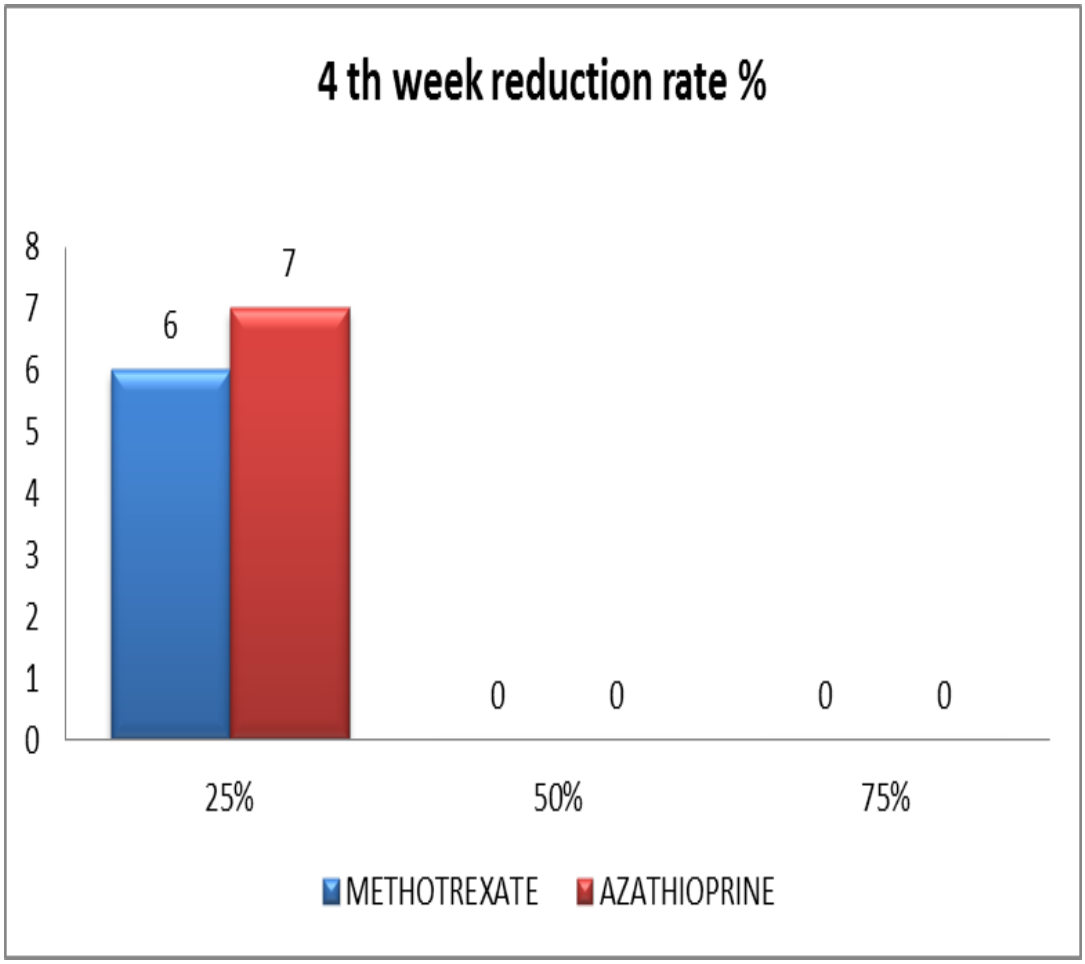


Chart 6 : Percentage reduction in PASI – 8th week

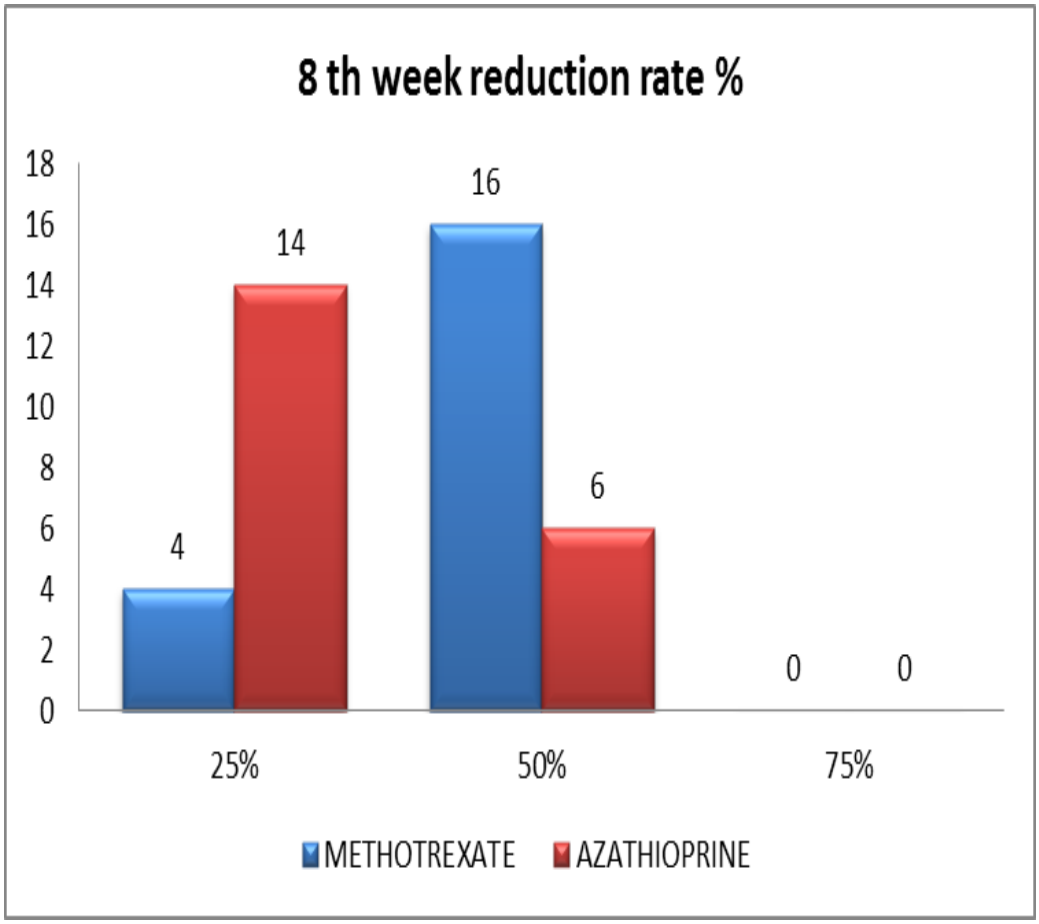
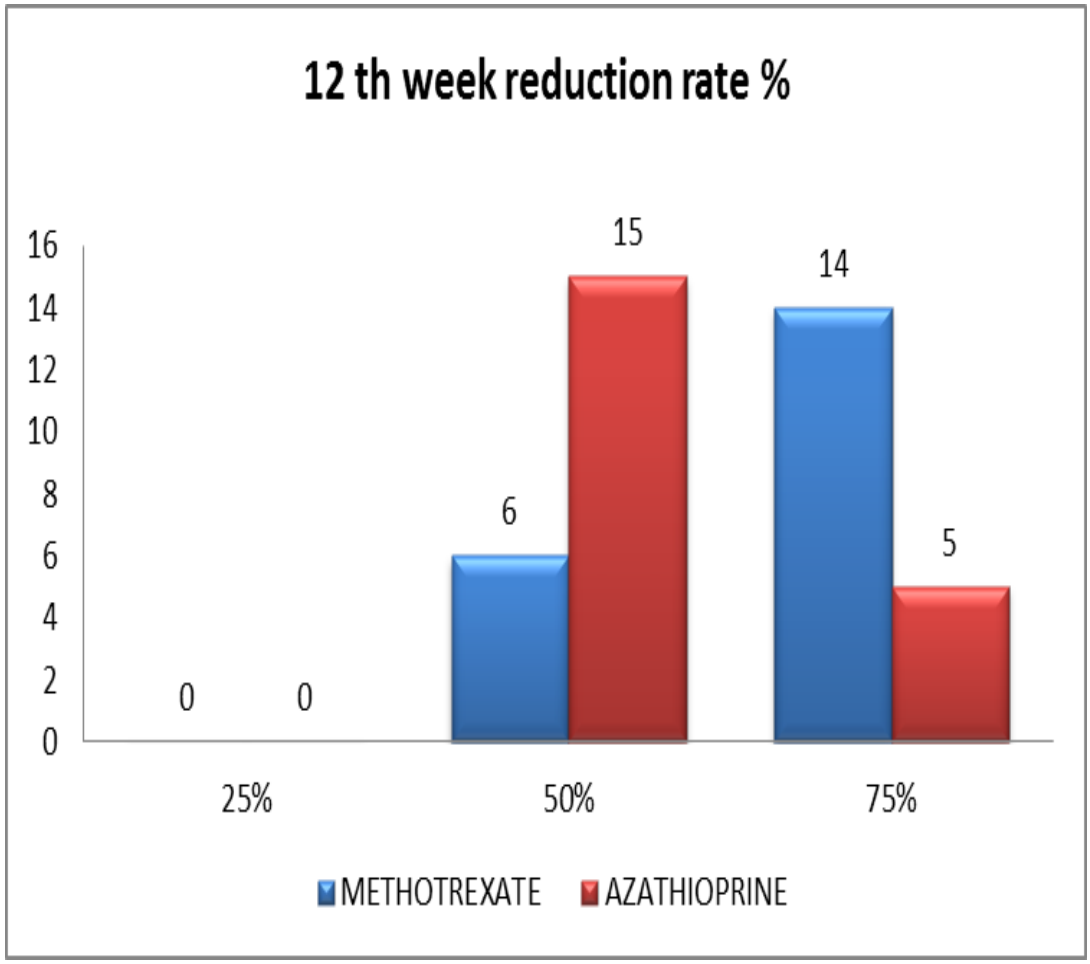


Chart 7 : Percentage reduction in PASI – 12th week



WEEK 12 Chi-Square test

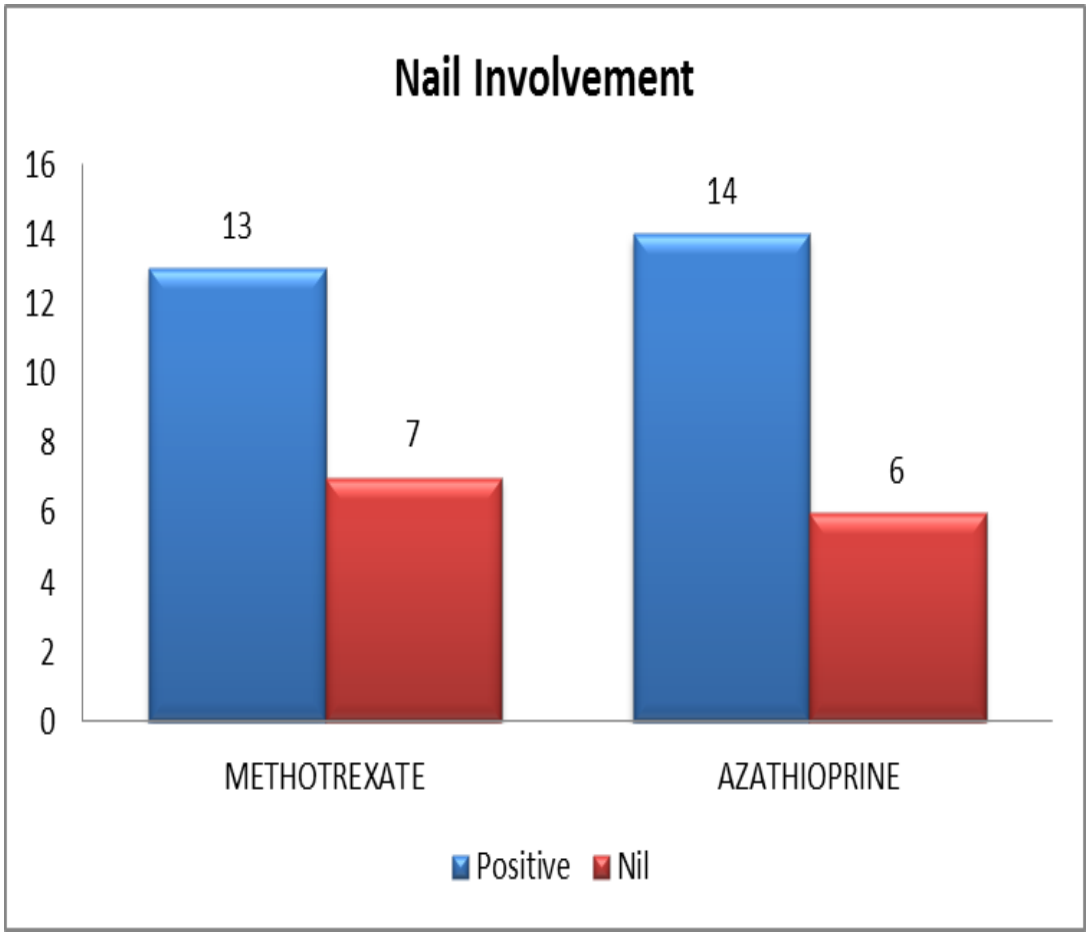
	Value	**df**	**Asymp.sig. (2-sided)**
Pearson Chi-Square	6.623[a]	2	.036
Likelihood Ratio	6.301	2	.043
Linear-by-Linear Association	6.193	1	.013
N of valid cases	19		

a. 5 cells (83.3%) have expected count less than 5. The minimum expected count is .26.

Table 6 : Response to treatment in both groups

Result	% PASI reduction at week 12	Methotrexate	Azathioprine
Excellent	>75%	14 (70%)	5 (25%)
Good	51-75%	6 (30%)	13 (65%)
Moderate	25-50%	0	2 (10%)
Poor	<25%	0	0

Chart 8 : Nail involvement in both groups



13 patients in Methotrexate groups and 14 patients in Azathioprine group were shown nail changes.

SAFETY AND TOLERABILITY

Overall 20% in the methotrexate group experienced adverse effects, but only 5% in Azathioprine group experienced it during the study period. (**p=0.151**)

Of the four patients in the Methotrexate group who developed adverse effects, two had gastritis, one had headache and one had diarrhoea. Patients who had gastrointestinal side effects, improved with proton pump inhibitors and folic acid. One who had headache tolerated the medication during subsequent weeks.

In Azathioprine group, one patient developed gastritis, but improved with proton pump inhibitors.

No significant haematological, dermatological, systemic adverse effects were observed in either of both groups during and follow up period of the study.

Likewise no specific adverse effects leading to withdrawal occurred in either of both the study groups. In general, both the drugs were well tolerated.

ADVERSE EFFECTS –CROSSTABULATION

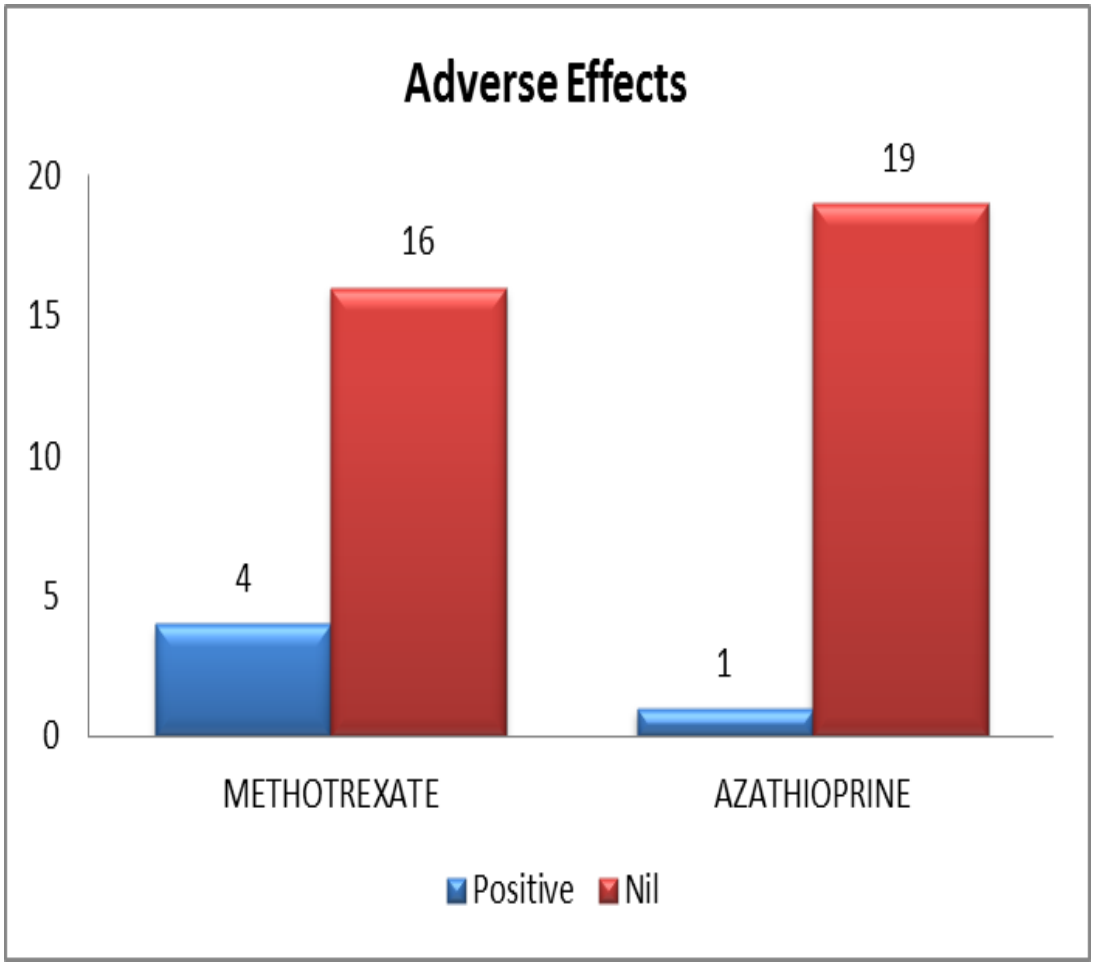
		MA		Total
		MEYHOTREXATE	AZATHIOPRINE	
AE	+ Count	4	1	5
	% within MA	20%	5%	12.5%
	Nil Count	16	19	35
	% within MA	80%	95%	87.5%
Total	Count	20	20	40
	% within MA	100%	100%	100%

CHI-SQUARE TEST

	Value	Df	Asymp. sig (2-sided)	Exact.sig (2-sided)	Exact.sig (1-sided)
Pearson Chi-Square	2.057[a]	1	.151		
Continuity correction[b]	.914	1	.339		
Likelihood ratio	2.185	1	.139		
Fisher's Exact Test				.342	.171
No of valid cases	40				

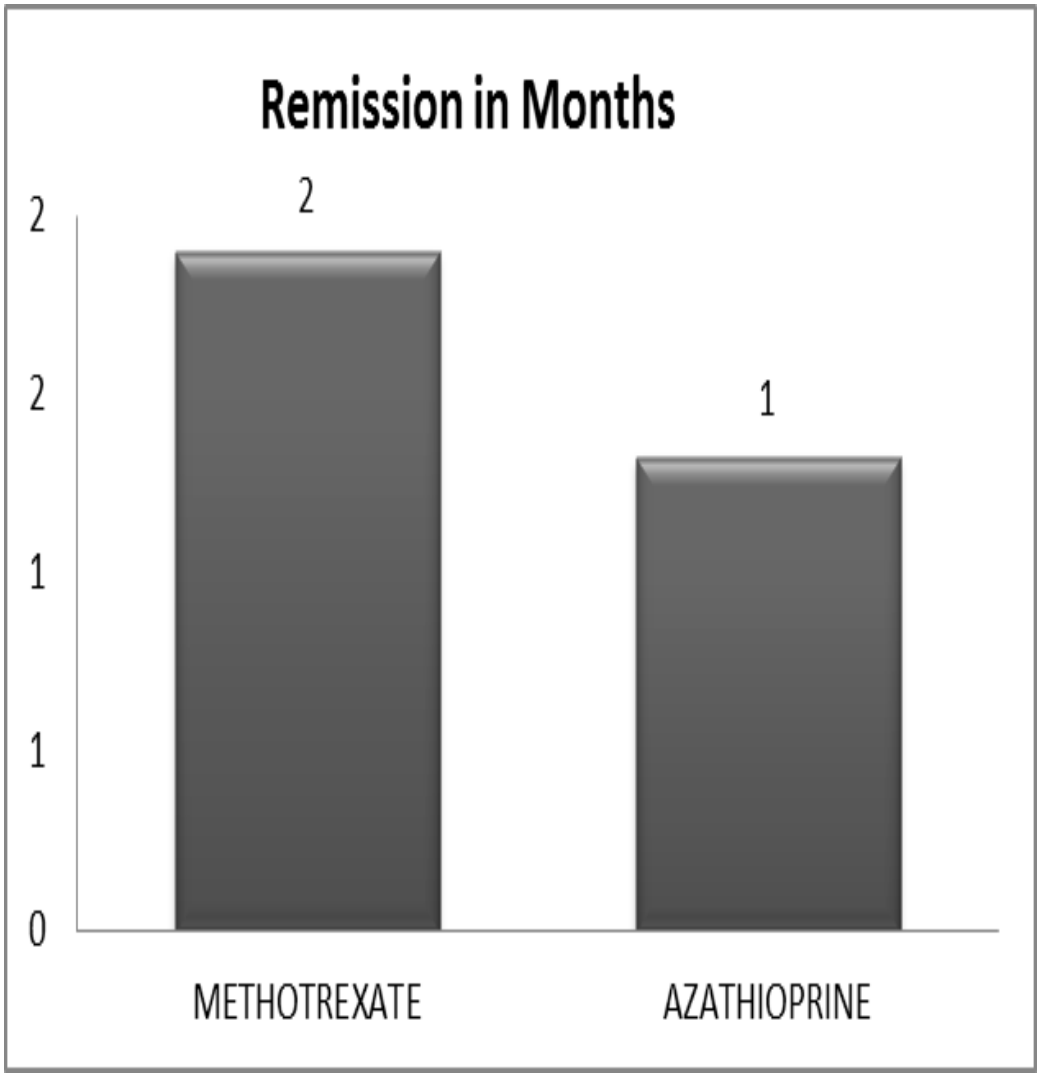
2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.50.

Chart9 : Adverse effects in both groups



Overall 20% in the methotrexate group experienced adverse effects, but only 5% in Azathioprine group experienced it during the study period. (**p=0.151)**

Chart 10 : Duration of remission in both groups



The mean duration of remission in Methotrexate group was 2 months whereas in Azathioprine group it was 1 month. (**p= 0.001**)

T-test

Group statistics

MA Remission	N	Mean	Standard deviation	Standard error
Methotrexate	20	1.900	.6407	.1433
Azathioprine	20	1.325	.3726	.0833

Independent sample test

Remission	Levene's test for equality of variance	T-test for equality Means							
	F	Sig.	T	Df	Mean difference	Sig (2-tailed)	Std. err.diff	95%confidence interval	
								lower	Upper
Equal variances assumed	4.164	.048	3.469	38	.5750	.01	.1657	.2395	.9105
Equal variances not assumed			3.469	30.531	.5750	.02	.1657	.2368	.9132

TREATMENT RESPONSE

METHOTREXATE

(GROUP A)

BEFORE TREATMENT

PATIENT 1

AFTER TREATMENT

BEFORE TREATMENT

PATIENT 2

AFTER TREATMENT

BEFORE TREATMENT

PATIENT 3

AFTER TREARMENT

BEFORE TREATMENT

PATIENT 4

AFTER TREATMENT

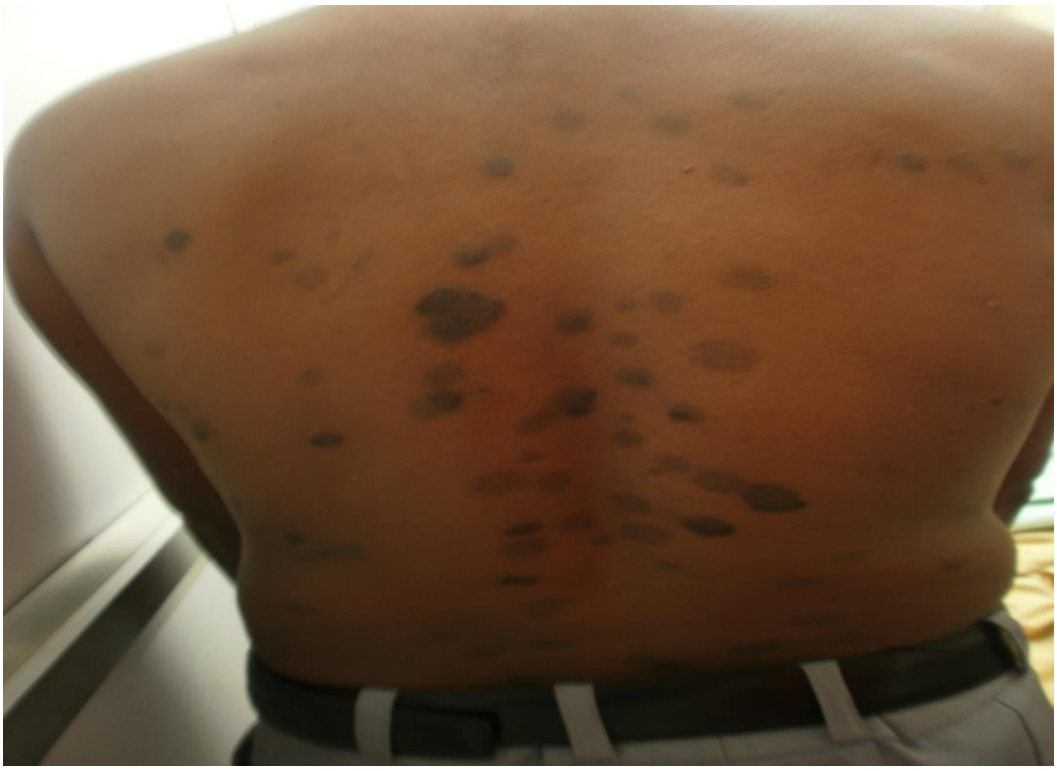
AZATHOPRINE

(GROUP B)

BEFORE TREATMENT

PATIENT 1

AFTER TREATMENT



BEFORE TREATMENT

PATIENT 2

AFTER TREATMENT

BEFORE TREATMENT

PATIENT 3

AFTER TREATMENT

BEFORE TREATMENT

PATIENT 4

AFTER TREATMENT

DISCUSSION

DISCUSSION

Psoriasis is a multisystem disorder with varying prevalence among different races of population in the world. Although various treatment modalities are available, no drug is curative for psoriasis. And the search for the safest, most efficacious and least toxic drug is still going on to provide a long-lasting relief from the disease.

Methotrexate

Methotrexate is not only efficacious in plaque type psoriasis, but also in psoriatic arthropathy, pustular psoriasis and psoriatic erythroderma. It is usually used in chronic plaque psoriasis where conventional treatment like topicals and phototherapy (including UVB and PUVA) were failed.

In our study the mean decrease in PASI score at week 12 in those who received T.Methotrexate 15mg/week was 74% (cumulative dose of 180 mg). At week 12, PASI 75 was achieved by 70% of the patients and rest of the 30% of the patients had achieved a minimum of PASI 50. The average duration of remission in this group was two months. Four out of twenty patients had developed adverse events.

This data correlates with various studies conducted namely,

1. A study by Heydendael et al[56], comparing the efficacy of Methotrexate and Cyclosporine in 85 patients with moderate to severe plaque psoriasis, showed that methotrexate administered at a dosage of at least 15 mg weekly for 16 weeks effectively cleared psoriasis. In this study, mean reduction in PASI from baseline after 16 weeks was 64%. PASI 75 was achieved by 60% of the patients at 16 weeks and the average period of remission was 6 weeks.

2. Sandhu et al[57]conducted one study, comparing Methotrexate and Cyclosporine in 30 consecutive patients with severe psoriasis, showed a more rapid clinical response, with a 69.4% improvement in mean PASI after one month of methotrexate therapy (mean dose of 27.7 mg weekly).

AZATHIOPRINE

Azathioprine is effectively used in the field of dermatology. There is a vast clinical experience of its use in the treatment of immuno-bullous disorders and as an adjuvant therapy to steroids.

But its usage in the treatment of psoriasis is not common. It has shown a relatively good safety profile as an immuno suppressive agent but there were only few studies available to know about its efficacy and safety in the treatment of psoriasis.

In our study, Azathioprine was used at a lower dose and the mean decrease in PASI score at week 12 in those who received T.Azathioprine 50mg/day was 62.1%. At week 12, PASI 75 was achieved by 25% of the patients and 65% of the patients had achieved of PASI 50.

10% of patients achieved PASI 25 at week 12.The average duration of remission in this group was one month. Only one of twenty patients in this group had developed adverse effect.

This data correlates with following studies conducted namely,

1. In a study by Du vivier et al[58], 29 patients were given high dose of Azathioprine upto 300 mg for 6 months. 66% of the patients had achieved PASI 75. In their study, leukopenia and deranged liver function tests necessitated discontinuation of treatment in 3 patients. But our study was of shorter duration and we administered lower dosages.

2. Another study by Greeves and Dawber[59], shown improvement of only 25% in PASI clearance in half of the patients. But their study lasted only for 6 weeks, as azathioprine need about 6 to 8 weeks for its maximal anti-proliferative effects on skin lesions.

There is only one published study comparing Methotrexate and Azathioprine in chronic plaque psoriasis.

In a study by Tariq malik and Amerejaz [60], which included 50 patients for a period of 8 weeks. In this study, group A received tablet methotrexate 10 mg weekly and group B received tablet azathioprine 50 mg thrice daily. PASI score was assessed at the start and end of the treatment. Patients were followed up for 4 weeks after the study.

PASI 75 was seen in 73% of patients in Methotrexate group while in Azathioprine group it was 27% patients at 8th week. And PASI 50 was achieved by 45% and 55% by Methotrexate and Azathioprine groups respectively. There were 5 drops out due to thrombocytopenia and deranged liver function tests.

The data of this study correlated with our study, particularly in achieving PASI 75 at week 12 by both the groups. And there was no drop out in our study.

In our study Methotrexate was more efficacious than Azathioprine in achieving PASI 75 at week 12 (70% vs 25%). Both the drugs were safer and tolerable while remission period in the Methotrexate group was longer than Azathioprine group.

CONCLUSION

CONCLUSION

- Methotrexate is more effective than Azathioprine in the treatment of chronic plaque psoriasis.
- Methotrexate had proven its efficacy in the management of psoriasis with many established trials and studies for more than 50 years.
- There were only few clinical studies of Azathioprine in the management of psoriasis.
- Even after introduction of newer agents like biologics, Methotrexate still remains the first line drug in the treatment of moderate to severe psoriasis.
- Advantage of both drugs were

- Lower cost
- Easy availability.
- Choice of oral administration.
- Easy monitoring with routine blood tests.
- Better patient compliance can be achieved.

- Main disadvantages of both the drugs were concurrence of systemic diseases such as severe infections like tuberculosis, renal disease, liver disorder and congestive cardiac failure. So these complications will preclude the use of the agents.

- Adverse effects associated with azathioprine are causally related, usually mild in severity and may resolve without a reduction in dosage.

- Azathioprine can be considered as an alternative treatment option in selected patients of chronic recalcitrant psoriasis when methotrexate can not be used.

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ANNEXURES

ANNEXURE I

GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL

DEPARTMENT OF DERMATOLOGY

PROFORMA

NAME : AGE :

SEX :

OCCUPATION : INCOME :

CHIEF COMPLAINTS :

H/O PRESENT ILLNESS :

Onset

Duration

H/O drug intake/ native treatment

H/O systemic symptoms

H/O active skin infections

PAST HISTORY

H/O Pulmonary tuberculosis/ diabetes/ hypertension/ bronchial asthma

H/O major medical/ surgical illness

FAMILY HISTORY :

H/O similar complaints in family members

PERSONAL HISTORY :

Diet :

Sleep :

Appetite :

Bowel and bladder habits :

Habits : smoking/ alcoholism

Menstrual history (in females) : menarche /menopause, cycles, flow

Obstetric history (in females) : pregnancy / abortions, lactation

Treatment history

H/O drug allergy

H/O prior systemic / phototherapy

GENERAL EXAMINATION :

Consciousness, orientation

Built and nourishment

Febrile / afebrile

Pallor / cyanosis / clubbing / icterus / lymphadenopathy / pedal edema

Pulse rate : Blood pressure :

Temperature : Respiratory rate :

SYSTEMIC EXAMINATION :

Cardiovascular system :

Respiratory system :

Abdomen :

Central nervous system :

LOCAL EXAMINATION :

Skin and mucosa :

Scalp and hair :

Palms and soles :

Nails :

PASI score :

Diagnosis :

INVESTIGATIONS :

CBC :Hb%	Blood glucose	ECG
TC	LFTS.	calcium, uric acid
DC	CXR &Mx test	Renal function test
ESR	HIV	VDRL

ANNEXURE II

CONSENT FORM

Mr / Mrs / Miss :

Age :

Address with phone :

I undersigned Mr / Mrs / Miss ---------- have been explained regarding above said study /procedure in my regional language. I am fully aware of the possible side effects and risks involved in this study / procedure. I am also aware of that this procedure may not always be successful and no guarantee can be made for successful outcome of the procedure.

I have been informed that this study / procedure will be performed by Dr.V.SRIDHAR.

I have also been explained that during this procedure if any complication arises, I may be given any emergency treatment best suitable without asking my prior permission.

I further state that I have carefully read and understood all the information provided in this form and with full conscious mind I hereby give my consent for the said study / procedure with its risk involved.

Signature of the patient / right thumb impression :

Signature of the Witness :

Date :

MASTER CHART

METHOTREXATE (GROUP A)

S.No	Age	Sex	Duration of illness (yrs)	P A S I S C O R E												Remission in months	Adverse effects	Nail involvement
				W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12			
1	23	M	2	16.9	16.9	14.4	14.4	12.7	10.3	8.8	6.9	5.2	5.2	4.2	4.2	2	Nil	Nil
2	48	M	6	17.7	17.0	17.0	14.4	12.8	10.9	10.9	8.8	7.8	7.8	6.4	4.0	1	Nil	+
3	45	M	10	15.6	15.6	13.0	13.0	10.0	8.5	8.5	7.1	6.1	5.9	5.9	3.7	2	Nil	+
4	37	M	6	15.0	15.0	13.3	12.3	11.9	7.8	6.7	6.7	5.2	5.2	3.9	3.0	3	+	+
5	48	M	2	19.3	17.0	17.0	15.8	13.0	11.5	11.5	10.2	10.2	9.8	6.8	4.8	1.5	Nil	Nil
6	30	M	4	14.9	14.9	12.6	10.5	9.9	7.2	6.0	5.0	5.0	4.6	4.6	3.2	2.5	Nil	Nil
7	41	M	4	16.8	15.1	14.4	14.4	12.4	10.1	10.1	9.8	8.0	8.0	6.8	4.1	2	Nil	+
8	42	M	3	16.0	14.2	13.4	10.4	10.4	8.9	7.9	7.9	6.4	6.0	5.0	3.9	1	Nil	+
9	52	M	8	12.3	11.8	10.1	9.6	8.2	7.0	7.0	6.3	6.3	5.9	4.2	2.8	1.5	+	+
10	41	M	5	17.4	15.9	14.0	12.4	10.9	8.8	8.8	7.4	7.4	6.2	6.6	4.0	2.5	Nil	+
11	50	M	8	21.8	20.8	19.6	18.4	16.4	14.5	12.0	12.0	10.7	9.4	7.6	6.6	3	Nil	+
12	39	M	3	13.2	12.7	12.7	10.5	9.1	8.1	7.5	7.5	7.5	6.5	6.5	5.9	1.5	Nil	Nil
13	64	M	9	18.0	17.1	17.1	14.4	12.8	11.6	10.2	8.9	8.9	7.2	5.2	4.5	2	+	+
14	54	M	11	14.6	11.6	10.1	10.0	9.1	8.5	8.5	7.0	6.6	5.9	5.9	3.1	1.5	Nil	+
15	32	M	3	19.1	18.3	16.4	13.4	12.2	10.7	9.2	9.2	8.1	8.1	8.1	7.4	1.5	Nil	Nil
16	57	M	4	12.5	12.0	11.1	9.7	9.7	8.9	7.0	7.0	5.8	5.8	5.8	4.4	2	Nil	+
17	60	F	7	18.4	17.4	15.0	13.4	11.3	11.3	9.3	8.1	7.7	6.3	5.6	4.1	2	+	+
18	29	F	2	15.2	15.2	13.6	11.9	9.9	8.2	7.5	6.8	6.8	5.9	5.9	3.4	3	Nil	Nil
19	48	F	8	13.2	12.2	10.9	10.9	9.2	8.8	6.5	5.0	4.2	4.2	3.8	3.0	1.5	Nil	+
20	31	F	4	15.3	14.3	12.0	12.0	10.3	8.3	6.1	6.1	5.8	4.5	3.7	3.7	1	Nil	Nil

AZATHIOPRINE (GROUP B)

S.No	Age	Sex	Duration of illness (yrs)	P A S I S C O R E												Remission in months	Adverse effects	Nail involve Ment
				W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12			
1	38	m	3	18.3	17.3	16.8	15.0	12.4	10.9	9.3	8.3	8.3	7.6	7.1	6.2	1.5	Nil	Nil
2	36	m	6	12.9	12.9	11.8	10.1	9.0	7.5	6.6	6.6	4.4	3.5	3.1	3.1	1	Nil	+
3	28	m	2	14.2	13.8	13.8	12.8	11.3	11.3	10.8	9.8	8.6	7.4	6.0	6.0	1	Nil	Nil
4	49	m	8	15.4	12.4	12.4	11.3	10.8	10.8	9.9	9.9	7.8	7.8	6.9	6.6	1.5	Nil	+
5	42	m	7	16.6	16.6	15.6	15.6	13.9	12.8	11.1	8.9	8.9	8.1	7.8	7.8	1	Nil	+
6	62	m	12	15.8	14.9	14.9	13.8	12.9	12.9	11.0	9.2	9.2	8.4	8.4	7.0	1	Nil	+
7	40	m	3	17.8	17.8	16.5	16.5	15.6	14.1	12.8	11.9	8.4	6.9	5.1	4.3	2	Nil	Nil
8	27	m	2	11.4	11.4	10.8	10.8	10.2	8.8	8.8	7.5	6.9	6.9	5.8	5.8	1	+	Nil
9	38	m	4	13.1	12.2	10.9	10.9	9.5	8.3	8.3	7.7	7.0	7.0	6.1	6.1	1.5	Nil	+
10	54	m	9	18.4	17.0	15.7	13.1	11.5	9.5	8.8	7.5	6.5	6.5	5.2	5.2	2	Nil	+
11	29	m	5	14.8	13.4	12.3	11.3	10.9	9.6	8.9	7.7	7.7	7.7	6.8	6.8	1.5	Nil	+
12	44	m	4	15.5	14.5	14.5	13.8	12.6	11.2	10.6	9.5	8.6	8.6	7.1	6.3	1	Nil	+
13	49	m	6	14.0	12.4	10.4	9.4	9.4	8.4	8.4	7.6	5.9	4.3	3.9	3.4	1	Nil	+
14	32	m	2	16.4	14.4	13.9	12.3	11.8	9.8	8.2	7.5	7.5	6.9	5.9	5.9	1	Nil	Nil
15	51	m	7	17.3	16.9	16.9	15.3	14.2	13.0	13.0	11.6	10.1	9.0	8.1	8.1	1	Nil	+
16	35	m	5	15.1	15.1	14.4	13.4	13.4	12.9	11.8	8.4	7.3	6.5	6.5	5.0	1.5	Nil	+
17	39	m	5	13.9	13.0	13.0	12.2	10.9	10.9	7.3	6.8	6.8	5.3	5.3	4.9	2	Nil	+
18	47	f	2	15.0	11.5	11.5	9.5	8.8	8.8	7.8	6.1	5.9	5.9	4.8	4.8	1.5	Nil	Nil
19	33	f	10	13.6	13.6	12.4	11.8	10.0	9.1	9.1	8.0	7.1	6.1	4.9	4.9	1	Nil	+
20	54	f	6	15.7	14.0	13.0	12.8	12.8	11.1	9.2	8.6	8.6	6.6	5.7	3.3	1.5	Nil	+